

22. A method according to claim 21 wherein the amount of the dose of the first active ingredient is from about 7 to 70 nmol.

Sub
C1
23. A method according to claim 1 wherein the amount of the dose of the second active ingredient is from about 0.1 to 5 μ mol.

Cont.
24. A method according to claim 1 wherein the amount of the dose of the second active ingredient is from about 0.15 to 4 μ mol.

25. A method according to claim 12 wherein the amount of the dose of formoterol fumarate dihydrate is from about 1 to 50 μ g.--

REMARKS

Claims 9 and 11-25 are pending in the case. Claim 9 has been amended. Claims 1-8 and 10 have been cancelled, and claims 11-25 added by the above amendment. No new matter has been introduced.

As Applicants' representative, Ms. Celia Leber, discussed with the Examiner by telephone on February 15, 2002, this response is essentially the same as the Second Preliminary Amendment filed on December 5, 2001. One change has been made in the claim amendments. Inadvertently, in the Second Preliminary Amendment there were two claims numbered claim 22. This error has been corrected by renumbering the second claim 22 and the following claims as claims 23-25. The Remarks have been revised slightly to delete the section on anticipation, an issue that was not raised in the office action mailed January 29, 2002, and to address the new secondary references cited in that office action.

Applicants submit herewith a Declaration of Lisa Woodson and a Declaration of Celia Leber, providing proof that the Second Preliminary Amendment and the accompanying Declaration of Jan Trofast were in fact hand-carried to the USPTO on December 5, 2001.

During the February 15th telephone conference with Ms. Leber, the Examiner indicated that if sufficient proof of filing were submitted, a subsequent office action, if required, would be made non-final. Accordingly, if the Examiner does not deem the application to be in condition

for allowance in view of this response, Applicants respectfully request that the next office action be made non-final.

Rejections Under 35 U.S.C. §§101 and 112

Claims 1-8 are rejected under 35 U.S.C. §§101 and 112. These claims have been cancelled, thereby obviating these rejections.

Rejection under 35 U.S.C. §102(b)

Claims 9-10 are rejected under 35 U.S.C. §103(a) as being unpatentable over WO 93/11733 (Carling) in view of Cazzola et al. (Reference U), Nederlands Tijdschrift voor Geneeskunde (Reference V) and Saunders Manual of Medical Practice (Reference W).

Claim 9 recites a method of treating chronic obstructive pulmonary disease (COPD) by administering to a patient formoterol (or a salt, a solvate of such a salt, or a solvate of formoterol) and budesonide.

Carling does not teach or suggest that his combination of formoterol and budesonide is suitable for treating COPD. Carling mentions that the combination is suitable for use in treating "respiratory diseases." The only specific respiratory disease that is mentioned in the Carling specification is asthma.

The suitability of the formoterol/budesonide combination for treating COPD would not have been obvious in view of Carling's general teaching of its use in treating respiratory diseases, even if this teaching could have been properly combined with the teachings, in References (U) and (V), respectively, that formoterol and budesonide alone would be useful in the treatment of COPD, and the mention in Reference (W) that COPD is a respiratory disease.

As set forth in the enclosed Declaration of Jan Trofast under 37 CFR §1.132, COPD refers to a group of disorders characterized by a progressive and generally irreversible limitation of airflow. COPD is a common disease in industrialized countries (for example, about 6 % of the men and 4 % of the women over 45 years in the UK are affected) and is responsible for a considerable morbidity and mortality. Most of the patients are smokers. The two most important conditions associated with COPD are chronic bronchitis and emphysema. Patients with chronic bronchitis exhibit frequent exacerbations due to recurrent infections.

Current treatment of COPD is often unsatisfactory. At present, COPD is often treated only in its more developed stages using a variety of inhaled or orally administered bronchodilators or inhaled anti-cholinergic agents. The problem with these treatments is that none of them has been regarded as effective. Smoking cessation has been shown to decrease the rate of decline in lung function, but the success of smoking-cessation programs is limited.

Airway inflammation in COPD differs from such inflammation in asthma. (Jeffery PK, Structural and Inflammatory Changes in COPD: a comparison with asthma. Thorax 1998;53:129-36. This and the other publications cited below are attached to the Declaration of Jan Trofast enclosed herewith). The beneficial influence of oral and inhaled corticosteroids is well established in patients with asthma. However, their usefulness in COPD is much less certain. Around the time of Applicants' invention, researchers were investigating the use of inhaled glucocorticoids such as budesonide in treating COPD. The results, discussed below, generally indicated that inhaled glucocorticoids were much less effective in treating COPD than in treating asthma.

One study reported that the overall effect of three years of treatment with budesonide on the forced expiratory volume (FEV) of patients with mild COPD was "quite limited as compared with the beneficial effects of inhaled glucocorticoids in asthma.... The small, overall, one-time beneficial effect on pulmonary function ... must be balanced against the risk of local and systemic side effects." Benefits were found to be only short-term, with no appreciable effect on the long-term progressive decline in lung function. (Pauwels et al., "Long-Term Treatment with Inhaled Budesonide in Persons with Mild Chronic Obstructive Pulmonary Disease Who Continue Smoking," The New England Journal of Medicine, 340:25, pp. 1948-1953, June 24, 1999.)

Another study found that the benefits of systemic glucocorticoids in treating acute exacerbations of COPD were much smaller than the benefits of glucocorticoids in the treatment of severe exacerbations of asthma. (Niewoehner, "Effect of Systemic Glucocorticoids on Exacerbations of Chronic Obstructive Pulmonary Disease," The New England Journal of Medicine, 340:25, pp. 1941-1947, June 24, 1999.)

Several articles at the time mentioned that the current treatments for COPD, including treatment with inhaled steroids, were unsatisfactory, and that new treatments were required.

(See, e.g., "Inhaled Steroids in COPD," The Lancet, Vol. 351, pp. 766-767, March 14, 1998, and "COPD: New Developments and Therapeutic Opportunities," Peter Norman, Drug News Perspect 11(7), September 1998.)

In view of this lack of enthusiasm in the field for treatment with budesonide, and also in view of the recognition in the art that asthma and COPD respond differently to treatment with budesonide, it would not have been obvious to the artisan that Carling's composition would be effective in the treatment of COPD. Moreover, in view of the great need for an effective treatment for COPD, if it had been obvious to Carling himself that his composition would have been effective in treating COPD, surely he would have mentioned this in his own disclosure.

In the parent application, the Examiner stated that, in the absence of unexpected results, it would have been obvious in view of the references cited in the parent (U.S. Patent No. 5,795,564 and CA 126:259329) to use budesonide and formoterol together to treat COPD. Applicants respectfully disagree, for the reasons discussed above, and also because Applicants have in fact obtained unexpected results.

As set forth in the enclosed Declaration of Jan Trofast under 37 CFR §1.132, about 800 patients with moderate to severe COPD were enrolled in a clinical trial. They were divided into four equal groups taking, respectively, budesonide/formoterol (as fumarate dihydrate)(2 x 160/4.5 µg bid, single inhaler), budesonide (2 x 200 µg bid), formoterol (as fumarate dihydrate) (2 x 4.5 µg bid) or a placebo for a period of 12 months. There was a significantly larger number of discontinuations in the placebo group than in the treated groups. The patients were monitored for severe exacerbations, and were tested at each clinical visit (8 times) for Forced Expiratory Volume (FEV₁). These parameters are typically used in evaluating the condition of a patient suffering from COPD.

A statistical analysis of the results of this study provided the following data:

Reduction in severe exacerbations (P-value):

Budesonide/formoterol against placebo	0.035
Budesonide/formoterol against formoterol	0.043
Budesonide/formoterol against budesonide	0.385

Improvement in forced expiratory volume (FEV₁) (P-value):

Budesonide/formoterol against placebo	< 0.001
Budesonide/formoterol against budesonide	< 0.001
Budesonide/formoterol against formoterol	0.487

The reduction of severe exacerbations was significantly ($p < 5\%$) greater for the patients treated with the budesonide/formoterol combination than for the placebo or the formoterol-treated groups. The study indicates that the number of exacerbations was 24 % lower for the patients treated with the combination than for the patients who received a placebo, and 23 % lower in comparison with formoterol-treated group.

The Forced Expiratory Volume of patients treated with the combination was significantly better ($p < 0.1\%$) for the patients treated with the combination than for the placebo or the budesonide-treated groups.

Together, the results obtained for these parameters indicate a significant improvement in both of the measured parameters for the budesonide/formoterol-treated patients, as compared to the patients treated with either budesonide alone or formoterol alone. Thus, the results of this study indicate, unexpectedly, that it is possible to treat even moderate to severe COPD patients with excellent, long-term results using the claimed method.

In view of the above, Applicants respectfully request that the rejection under 35 U.S.C. §103 be withdrawn.

Conclusion

Attached is a marked-up version of the changes being made by the current amendment.

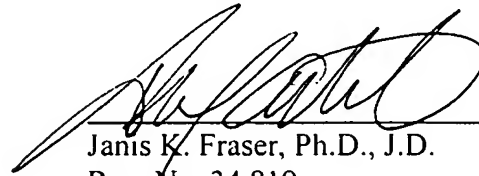
Applicant : Carl-Axel Bauer et
Serial No. : 10/010,283
Filed : November 13, 2001
Page : 8

Attorney's Docket No. 06275-150003 / D 1841-3P US

Applicants ask that all claims be allowed. Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: April 25, 2002



Reg. No. 30, 175

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin St.
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

Version with markings to show changes made

In the claims:

Claims 1-8 and 10 have been cancelled.

Claim 9 has been amended as follows:

9. (Amended) A method for the treatment of a patient suffering from chronic obstructive pulmonary disease, which method comprises administering to the patient via inhalation, simultaneously, sequentially or separately, a therapeutically effective amount of (i) a dose of a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and (ii) a dose of a second active ingredient which is budesonide, [and] wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:2500 to 12:1.



COPY OF PAPERS
ORIGINALLY FILED

Applicant's Docket No.: 06275-150003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Carl-Axel Bauer et al.
Serial No. :
Filed : November 13, 2001
Title : NEW USE FOR BUDESONIDE AND FORMOTEROL

Art Unit : 1614
Examiner : R. Cook

RECEIVED

MAY 09 2002

Commissioner for Patents
Washington, D.C. 20231

TECH CENTER 1600/2900

SECOND PRELIMINARY AMENDMENT

This application is a continuation of USSN 09/670.457. In response to the action mailed in the parent application on May 10, 2001, please amend the application as follows:

In the claims:

Cancel claims 1-8 and 10.

Amend claim 9 as follows:

9. (Amended) A method for the treatment of a patient suffering from chronic obstructive pulmonary disease, which method comprises administering to the patient via inhalation, simultaneously, sequentially or separately, a therapeutically effective amount of (i) a dose of a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and (ii) a dose of a second active ingredient which is budesonide, wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:2500 to 12:1.

Add new claims 11- 24.

-- 11. A method according to claim 9, wherein the first and/or second active ingredient is used in admixture with one or more pharmaceutically acceptable additives, diluents and/or carriers.

CERTIFICATE OF DELIVERY BY HAND

I hereby certify that this correspondence is being delivered by hand on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

Date of Delivery

Signature

Typed or Printed Name of Person Signing Certificate

12. A method according to claim 9, wherein the first active ingredient is formoterol fumarate dihydrate.

13. A method according to claim 9, wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:555 to 2:1.

14. A method according to claim 13 wherein the molar ratio is from 1:70 to 1:4.

15. A method according to claim 9 further comprising providing the doses to the patient in the form of a dry powder.

16. A method according to claim 15 wherein the first and second active ingredients are formulated as powder particles having a mass median diameter of less than 10 μm .

17. A method according to claim 9 wherein the first and second active ingredients are provided in the form of an admixture.

18. A method according to claim 9 wherein the doses are administered separately, less than about 2 hours apart.

19. A method according to claim 18 wherein the doses are administered separately, less than about 30 minutes apart.

20. A method according to claim 19 wherein one dose is administered immediately after the other.

21. A method according to claim 9 wherein the amount of the dose of the first active ingredient is from about 2 to 120 nmol.

22. A method according to claim 21 wherein the amount of the dose of the first active ingredient is from about 7 to 70 nmol.

22. A method according to claim 1 wherein the amount of the dose of the second active ingredient is from about 0.1 to 5 μmol .

23. A method according to claim 1 wherein the amount of the dose of the second active ingredient is from about 0.15 to 4 μmol .

24. A method according to claim 12 wherein the amount of the dose of formoterol fumarate dihydrate is from about 1 to 50 μg --

REMARKS

Claims 9 and 11-24 are pending in the case. Claims 1-8 and 10 have been cancelled and claims 11-24 added by the above amendment. No new matter has been introduced.

Claims 1-8 are rejected under 35 U.S.C. §§101 and 112. These claims have been cancelled, thereby obviating these rejections.

Claims 9-10 are rejected under 35 U.S.C. §102(b) as being anticipated by WO 93/11733 (Carling). Claims 9-10 are also rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,795,564 and CA 126:259329. These rejections will be addressed in turn.

Rejection under 35 U.S.C. §102(b)

Claim 9 recites a method of treating chronic obstructive pulmonary disease (COPD) by administering to a patient formoterol (or a salt, a solvate of such a salt, or a solvate of formoterol) and budesonide.

Carling does not teach or suggest that his combination of formoterol and budesonide is suitable for treating COPD. Carling mentions that the combination is suitable for use in treating "respiratory diseases." The only specific respiratory disease that is mentioned in the Carling specification is asthma.

It is axiomatic that anticipation requires that every limitation of a claim at issue be disclosed in a single prior art reference. It is also well established that the disclosure of a broad genus (such as treatment of respiratory diseases) does not anticipate a claim limited to a species (such as treatment of COPD).

A situation analogous to that in the present application was considered by the Federal Circuit in *Corning Glass Works v. Sumitomo Electric*, 868 F.2d 1251, 9 USPQ2d 1962 (CAFC 1989). In *Corning Glass Works*, the court considered whether Corning's claim, directed to an optical fiber having a fused silica core doped with germania, was anticipated by a Japanese application. The Japanese application disclosed optical fibers with doped cores, but did not specifically teach germania as a dopant. Sumitomo argued that Corning's claim was invalid, because the Japanese reference disclosed fibers having doped cores, listed polyvalent metal

oxide dopants, and did not exclude germania. The court stated that this argument was "wholly meritless" because "under Sumitomo's theory, a claim to a genus would inherently disclose all species." The court found that the Corning claim was not anticipated, because "the Japanese application is a reference only for that which it teaches." *Id.*, p. 1262.

Nor would the suitability of the formoterol/budesonide combination for treating COPD have been obvious in view of Carling's general teaching of its use in treating respiratory diseases.

As set forth in the enclosed Declaration of Jan Trofast under 37 CFR §1.132, COPD refers to a group of disorders characterized by a progressive and generally irreversible limitation of airflow. COPD is a common disease in industrialized countries (for example, about 6 % of the men and 4 % of the women over 45 years in the UK are affected) and is responsible for a considerable morbidity and mortality. Most of the patients are smokers. The two most important conditions associated with COPD are chronic bronchitis and emphysema. Patients with chronic bronchitis exhibit frequent exacerbations due to recurrent infections.

Current treatment of COPD is often unsatisfactory. At present, COPD is often treated only in its more developed stages using a variety of inhaled or orally administered bronchodilators or inhaled anti-cholinergic agents. The problem with these treatments is that none of them has been regarded as effective. Smoking cessation has been shown to decrease the rate of decline in lung function, but the success of smoking-cessation programs is limited.

Airway inflammation in COPD differs from such inflammation in asthma. (Jeffery PK. Structural and Inflammatory Changes in COPD: a comparison with asthma. *Thorax* 1998;53:129-36. This and the other publications cited below are attached to the Declaration of Jan Trofast enclosed herewith). The beneficial influence of oral and inhaled corticosteroids is well established in patients with asthma. However, their usefulness in COPD is much less certain. Around the time of Applicants' invention, researchers were investigating the use of inhaled glucocorticoids such as budesonide in treating COPD. The results, discussed below, generally indicated that inhaled glucocorticoids were much less effective in treating COPD than in treating asthma.

One study reported that the overall effect of three years of treatment with budesonide on the forced expiratory volume (FEV) of patients with mild COPD was "quite limited as compared

with the beneficial effects of inhaled glucocorticoids in asthma.... The small, overall, one-time beneficial effect on pulmonary function ... must be balanced against the risk of local and systemic side effects." Benefits were found to be only short-term, with no appreciable effect on the long-term progressive decline in lung function. (Pauwels et al., "Long-Term Treatment with Inhaled Budesonide in Persons with Mild Chronic Obstructive Pulmonary Disease Who Continue Smoking," The New England Journal of Medicine, 340:25, pp. 1948-1953, June 24, 1999.)

Another study found that the benefits of systemic glucocorticoids in treating acute exacerbations of COPD were much smaller than the benefits of glucocorticoids in the treatment of severe exacerbations of asthma. (Niewoehner, "Effect of Systemic Glucocorticoids on Exacerbations of Chronic Obstructive Pulmonary Disease," The New England Journal of Medicine, 340:25, pp. 1941-1947, June 24, 1999.)

Several articles at the time mentioned that the current treatments for COPD, including treatment with inhaled steroids, were unsatisfactory, and that new treatments were required. (See, e.g., "Inhaled Steroids in COPD," The Lancet, Vol. 351, pp. 766-767, March 14, 1998, and "COPD: New Developments and Therapeutic Opportunities," Peter Norman, Drug News Perspect 11(7), September 1998.)

In view of this lack of enthusiasm in the field for treatment with budesonide, and also in view of the recognition in the art that asthma and COPD respond differently to treatment with budesonide, it would not have been obvious to the artisan that Carling's composition would be effective in the treatment of COPD. Moreover, in view of the great need for an effective treatment for COPD, if it had been obvious to Carling himself that his composition would have been effective in treating COPD, surely he would have mentioned this in his own disclosure.

Rejection under 35 U.S.C. §103

The Examiner states that, in the absence of unexpected results, it would have been obvious in view of the cited references (U.S. Patent No. 5,795,564 and CA 126:259329) to use budesonide and formoterol together to treat COPD. Applicants respectfully disagree, for the reasons discussed above, and also because Applicants have in fact obtained unexpected results.

As set forth in the enclosed Declaration of Jan Trofast under 37 CFR §1.132, about 800 patients with moderate to severe COPD were enrolled in a clinical trial. They were divided into four equal groups taking, respectively, budesonide/formoterol (as fumarate dihydrate) (2 x 160/4.5 µg bid, single inhaler), budesonide (2 x 200 µg bid), formoterol (as fumarate dihydrate) (2 x 4.5 µg bid) or a placebo for a period of 12 months. There was a significantly larger number of discontinuations in the placebo group than in the treated groups. The patients were monitored for severe exacerbations, and were tested at each clinical visit (8 times) for Forced Expiratory Volume (FEV_1). These parameters are typically used in evaluating the condition of a patient suffering from COPD.

A statistical analysis of the results of this study provided the following data:

Reduction in severe exacerbations (P-value):

Budesonide/formoterol against placebo	0.035
Budesonide/formoterol against formoterol	0.043
Budesonide/formoterol against budesonide	0.385

Improvement in forced expiratory volume (FEV_1) (P-value):

Budesonide/formoterol against placebo	< 0.001
Budesonide/formoterol against budesonide	< 0.001
Budesonide/formoterol against formoterol	0.487

The reduction of severe exacerbations was significantly ($p < 5\%$) greater for the patients treated with the budesonide/formoterol combination than for the placebo or the formoterol-treated groups. The study indicates that the number of exacerbations was 24 % lower for the patients treated with the combination than for the patients who received a placebo, and 23 % lower in comparison with formoterol-treated group.

The Forced Expiratory Volume of patients treated with the combination was significantly better ($p < 0.1\%$) for the patients treated with the combination than for the placebo or the budesonide-treated groups.

Together, the results obtained for these parameters indicate a significant improvement in both of the measured parameters for the budesonide/formoterol-treated patients, as compared to the patients treated with either budesonide alone or formoterol alone. Thus, the results of this

study indicate, unexpectedly, that it is possible to treat even moderate to severe COPD patients with excellent, long-term results using the claimed method.

Conclusion

Attached is a marked-up version of the changes being made by the current amendment.

Applicants ask that all claims be allowed. Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date:

Dec 4, 2001

Janis K. Fraser

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34.819

Fish & Richardson P.C.
225 Franklin St.
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

Version with markings to show changes made

In the claims:

Claims 1-8 and 10 have been cancelled.

Claim 9 has been amended as follows:

9. (Amended) A method for the treatment of a patient suffering from chronic obstructive pulmonary disease, which method comprises administering to the patient via inhalation, simultaneously, sequentially or separately, a therapeutically effective amount of (i) a dose of a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and (ii) a dose of a second active ingredient which is budesonide, [and] wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:2500 to 12:1.

Thorax

The Journal of the British Thoracic Society

DO NOT REMOVE
FROM LIBRARY

Editorials

- 79 Sputum induction to assess airway inflammation: is it an inflammatory stimulus?
I D Pavord
- 81 Is the lung important as a privileged site for the human immunodeficiency virus?
J R Clarke, D M Mitchell, R J Coker, D Israel-Biet

Original articles

- 83 Changes in sputum composition between two inductions performed on consecutive days
O Holz, K Richter, R A Jörres, P Speckin, M Mücke, H Magnussen
- 87 Effect of repeated sputum induction on cell counts in normal volunteers *J A Nightingale, D F Rogers, P J Barnes*
- 91 Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma *A Jatakanon, S Lim, S A Kharitonov, K F Chung, P J Barnes*
- 96 Measurement of sniff nasal and diaphragm twitch mouth pressure in patients
P D Hughes, M I Polkey, D Kyrrousis, C-H Hamnegard, J Moxham, M Green
- 101 Asthma and airway hyperresponsiveness among Belgian conscripts, 1978-91
P Dubois, E Degraze, O Vandenplas
- 106 Radiofrequency resection of bronchial tumours in combination with cryotherapy: evaluation of a new technique *A Marasso, V Bernardi, R Gai, E Gallo, G M Massaglia, M Onoscuri, S B Cardaci*

Short paper

- 110 Effect of an inhaled glucocorticosteroid on mast cell and smooth muscle β_2 adrenergic tolerance in mild asthma *D H Yates, M Worsdell, P J Barnes*

Science matters

- 114 Secretory leukoprotease inhibitor: a native antimicrobial protein presenting a new therapeutic option? *J F C Tomee, G H Koeter, P S Hiemstra, H F Kauffman*

Review series

- 117 Health effects of passive smoking - 5: Parental smoking and allergic sensitisation in children *D P Strachan, D G Cook*
- 124 Lung infections - 2: *Branhamella catarrhalis*: epidemiological and clinical aspects of a human respiratory tract pathogen *T F Murphy*

Occasional reviews

- 129 Structural and inflammatory changes in COPD: a comparison with asthma *P K Jeffery*
- 137 New therapies for chronic obstructive pulmonary disease *P J Barnes*

Case reports

- 148 Commentary *F L Raymond*
- 149 Opitz oculo-genito-laryngeal syndrome: a rare cause of recurrent aspiration pneumonia in an adult *D de Silva, A Osborne, S A Simpson, J C S Dean, A Seaton*
- 151 Familial primary spontaneous pneumothorax consistent with true autosomal dominant inheritance *P J Morrison, R C Lowry, N C Nevin*
- 152 Can reactive airways dysfunction syndrome (RADS) transform into occupational asthma due to "sensitisation" to isocyanates? *C Leroy, L Perfetti, A Cartier, J-L Malo*

Letters to the editor

- 154 Atopy phenotype *S Thomas, N Morton, S Holgate, J Hopkin* • Lung volume reduction surgery *M D L Morgan, D A Waller, S J Singh, D A Lomas, N Caine, F C Wells*

Miscellaneous

- 155 Book review • Notice

The illustration on the front cover is from the article entitled "Structural and inflammatory changes in COPD: a comparison with asthma" by P K Jeffery which appears on pp 129-136.

Structural and inflammatory changes in COPD: a comparison with asthma

Peter K Jeffery

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. In Europe COPD and asthma, together with pneumonia, are the third most common cause of death. In North America COPD is the fourth leading cause of death, and mortality rates and prevalence are increasing. The incidence and morbidity from COPD are rising. The main risk factors are cigarette smoking and occupational exposure. Part of the reason for the slow advance in our understanding has been the difficulty of distinguishing, with certainty, the difference between subjects with COPD who may show a degree of airways reversibility and those older subjects with asthma whose reversible airflow obstruction has become more "fixed". There may also be mixtures of COPD and asthma which co-exist in any one patient (fig 1).

For the purpose of the present synopsis the definitions of COPD and asthma are those included in the recently published ERS and ATS guidelines;¹⁻³ there is, however, much debate and the clinical definitions are still imprecise. The difficulties of definition are compounded by the recognition that both COPD and asthma are not disease entities but, rather, each is probably a complex of conditions which contribute to airflow limitation (*syn* obstruction). In asthma, airflow limitation is usually variable over short periods of time and reversible, although an underlying irreversible component may develop when inflammation

persists in association with repeated allergen or occupational exposure; extrinsic (allergic) and intrinsic (late onset) and occupational forms are recognised. In COPD the limitation, particularly to expiratory airflow, is usually, but not always, persistent and typically shows a more rapid progressive deterioration with age than is normal. Accordingly, the most recent and generally accepted definition in Europe is: "Chronic obstructive pulmonary disease (COPD) is a disorder characterised by reduced maximum expiratory flow and slow forced emptying of the lungs; features which do not change markedly over several months".¹ Three conditions may contribute to airflow limitation to varying degrees in each patient:

(1) Chronic bronchitis (mucus hypersecretion) which is defined as the presence of chronic cough and recurrent increases in bronchial secretions sufficient to cause expectoration. The secretions are present on most days for a minimum of three months a year, for at least two successive years, and cannot be attributed to other pulmonary or cardiac causes.⁴⁻⁶ Chronic bronchitis can occur in the absence of airflow limitation.

(2) Adult chronic bronchiolitis (small or peripheral airways disease) which is difficult to define clinically but may be recognised by sophisticated tests of function of the small airway - that is, airways of 2 mm diameter or less.⁷⁻⁹

(3) Emphysema which is defined anatomically by permanent, destructive enlargement of airspaces distal to terminal bronchioli without obvious fibrosis.⁹ However, the presence or absence of an ongoing fibrotic process is still debated (see below).

The airways in chronic bronchitis and COPD are also markedly inflamed; however, in contrast to asthma the predominant type of inflammatory cell and the main anatomical site of the lesion appear to differ.¹⁰

The following synopsis focuses on the structural changes and the inflammation of conducting airways and lung in COPD and briefly makes comparisons with what is known in asthma. For further details of the effects of smoking and comparisons of COPD with asthma the reader is referred elsewhere.¹¹⁻¹³

Pathology

PROXIMAL BRONCHI (CHRONIC BRONCHITIS): Cough and sputum production are the symptoms most frequently experienced by smokers:

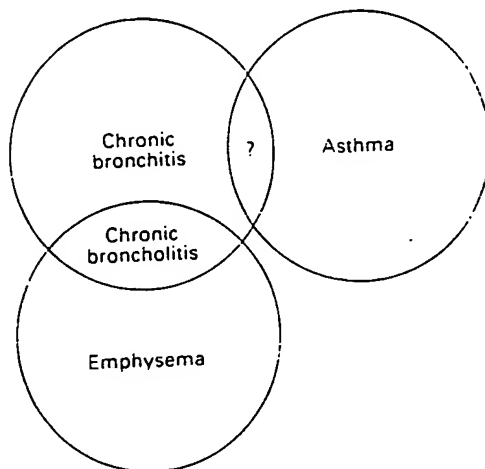


Figure 1 Airflow limitation: simplified interrelationships between COPD and asthma.

Imperial College
School of Medicine at
the National Heart
and Lung Institute,
London, UK
P K Jeffery

Correspondence to
Dr P K Jeffery, Lung
Pathology Unit, Royal
Brompton Hospital, Sydney
Street, London SW3 6NP,
UK

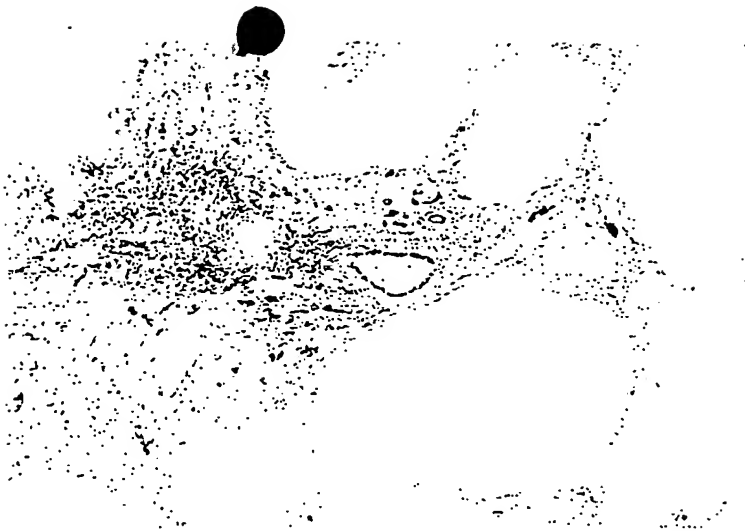


Figure 7 Histological section of alveolar region in a case of COPD in which there are enlarged alveolar spaces surrounding a small airway with marked peribronchiolitis. Stain: haematoxylin and eosin (courtesy of Professor B Gornin).

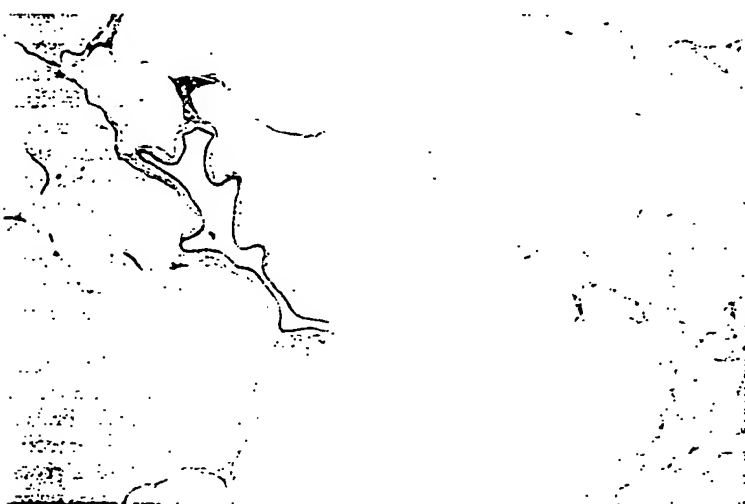


Figure 8 Section of emphysematous lung in which there is destruction of alveolar attachments to the bronchiolar wall, resulting in its tortuous appearance and early collapse during expiration. Stain: haematoxylin and eosin.

may underlie the development of centriacinar emphysema.

EMPHYSEMA

The early changes of emphysema have been thought to include subtle disruption to elastic fibres with accompanying loss of elastic recoil, bronchiolar and alveolar distortion (see fig 8), and the appearance of fenestrae which enlarge,^{32,33} an alteration which has been referred to as "microscopic" emphysema (fig 9). These biochemical and microscopic changes lead to loss, by destruction of the elastic framework, of the interalveolar septa and the macroscopic appearance of spaces of more than 1 mm in diameter. Recent data have shown that this destructive process is accompanied by a net increase in the mass of collagen which suggests that, contrary to the current internationally accepted definition (see above), there is active alveolar wall fibrosis in the tissue which remains even in otherwise emphysematous lungs.³⁴

Two main morphological forms of emphysema have been described. They are distinguished anatomically by the region of the acinus which is destroyed. Centriacinar (or centrilobular) emphysema is characterised by focal destruction restricted to respiratory bronchioli and the central portions of the acinus, each focus surrounded by areas of grossly normal lung parenchyma. This form of emphysema is usually more severe in the upper lobes of the lung (fig 10). Panacinar (or panlobular) emphysema involves destruction of the walls, in a fairly uniform manner, of all the air spaces beyond the terminal bronchiolus. The panacinar form is characteristic of patients who develop smoking-related emphysema relatively early in life and, in contrast to the centriacinar form, has a tendency to involve the lower lobes more than the upper. In the familial form of panacinar emphysema it is usually associated with deficiency of alpha₁-antitrypsin³⁵ which normally protects the respiratory region by forming a highly effective anti-elastase screen. These distinct morphological forms are thought to have distinct functional properties.³²

Epidemiological studies have demonstrated a significant relationship between cigarette smoking and severity of emphysema³³ but the mechanism(s) by which cigarette smoke causes such damage is still the subject of much speculation. The working hypothesis has been that emphysema is the result of an imbalance between proteolytic enzymes and protease inhibitors in the lung, favouring an excess of enzyme and, in particular, elastases. In addition, the imbalance between oxidants and antioxidants also contributes by allowing an excessive oxidant burden to degrade the normal protease inhibitor screen.^{34,35} The proposed mechanism involves interactions between cigarette smoke, alveolar macrophages, chemottractants, neutrophils, elastases, endogenous and exogenous oxidants, protease inhibitors, antioxidants, and lung connective tissue, primarily elastin, which undergoes repeated destruction, synthesis, and degradation.³⁶

Whilst the major pathological changes of COPD are thought to occur in the airways and lung parenchyma in patients with advanced COPD, changes also occur to the pulmonary circulation, the right heart, and respiratory muscles.³⁷ With alveolar hypoxia the medial vascular smooth muscle of pulmonary arterioles extends distally to vessels that normally lack muscle and there is intimal thickening. In addition, loss of the vascular bed occurs as a consequence of emphysema. Right ventricular enlargement due to dilatation and/or hypertrophy is not uncommon and atrophy of the diaphragm occurs in some cases of COPD. Whilst emphysema and right ventricular hypertrophy are common in COPD, both are uncommon findings in asthma.

Cellular infiltrate

Niewoehner and co-workers³⁸ and Cosio and colleagues³⁹ were among the first to describe the inflammation of the respiratory region in smokers dying suddenly: inflammation in bron-

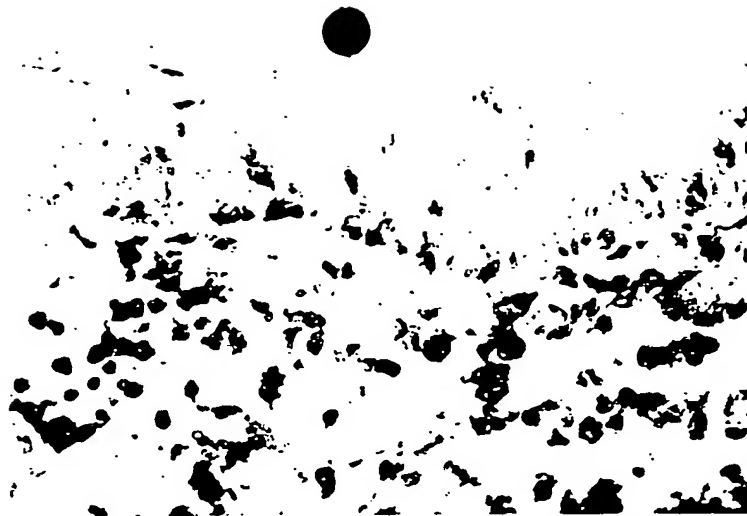


Figure 11 Histological section of a mucosal biopsy specimen taken by flexible fiberoptic bronchoscopy from a patient with an exacerbation of bronchitis. There are large numbers of CD45+ leucocytes infiltrating the subepithelial zone and fewer within the squamoid surface epithelium. (Immunostained by Dr Li using the APAP technique and new fuchsin to stain the CD45+ cells red; biopsy specimen kindly obtained by Dr Suetta.)

Table 1 Fold increases (compared with healthy controls) in subjects with chronic bronchitis alone (CB) or with airflow limitation (CB + COPD) and atopic asthma

	CB	CB + COPD	Asthma
CD45+	2.2	2.3	2
CD3+	2.3	4.0	2
CD4+	2	2.8	2.5
CD8+	3	8.4	2
CD4:CD8+	1:4	1:2	3:1
Neutrophil	2	2.2	-1.5
Eosinophil	1.7	3.5	93
Macrophage	4.5	8.6	±

creased in the surface epithelium as did T lymphocytes and macrophages in the subepithelium. We found that it is the CD8+ lymphocyte subset which increases in number and proportion in COPD and the increase of CD8+ cells shows a significant association with decline in lung function.¹⁰ This contrasts with the predominance and activation of the CD4+ T cell subset which is the characteristic change of mild atopic asthma. Interestingly, the high numbers of neutrophils found in lavage fluid from subjects with COPD⁷⁸ is not reflected in their numbers in the bronchial mucosa, at least in the subepithelial zone (often referred to as the lamina propria) which is the zone usually quantified in bronchial biopsies.¹⁰⁻¹²

Table 2 Simplified comparison of COPD and asthma

	COPD	Asthma
Airflow obstruction	Progressive deterioration of lung function (irreversible component)	Variable (± irreversible component)
Post mortem	Excessive mucus (mucoid/purulent), small airway disease, emphysema	Hyperinflation, airway plugs exudate - mucus, no or little emphysema
Sputum	Macrophage, neutrophil (infective exacerbation)	Eosinophilia, metachromatic cells, Cretia bodies
Surface epithelium	Fragility undetermined	Fragility loss
Bronchiolar mucous cells	Metaplasia/hyperplasia	Mucous metaplasia is debated
Reticular basement membrane	Variable or normal	Homogeneously thickened and hyaline
Congestion/oedema	Variable/fibrotic	Present
Bronchial smooth muscle	Enlarged mass (small airways)	Enlarged mass (large airways)
Bronchial glands	Enlarged mass (increased acidic glycoprotein)	Enlarged mass (no change in mucin histochemistry)
Cellular infiltrate	Predominantly CD3, CD8, CD68, CD25, VLA-1 and HLA-DR -ve, mild eosinophilia, not degranulated, mast cell increase	Predominantly CD3, CD4, CD25 (IL-2R) -ve, marked eosinophilia (EG2 -ve), degranulated, mast cell increase, decrease in severe ataxia
Cytokines (ISH)	GM-CSF protein ± IL-4 but not IL-5	IL-4 - IL-5 gene expression, Th2 profile

Reproduced with permission from reference 39.

The relative changes in each cell immunophenotype in chronic bronchitis or COPD, compared with their respective values in asthma and in normal healthy subjects, are summarised in table 1. Comparative studies of the distinct patterns of interleukin and cytokine gene expression in COPD and asthma are now urgently needed.

Concluding comments

Table 2 summarises the main distinctions between COPD and asthma. There is evidence of inflammation in both conditions but there are considerable differences in terms of the predominant phenotype and the site and functional consequences of such inflammation. At this stage in our knowledge the distinctions do not appear to be absolute. However, the author believes that by rigorous recordings of clinical data, careful application of the histological, cytological, immunological and molecular techniques now available, it will be possible for biopsy specimens of conducting airways to provide for differential diagnosis and the monitoring of either disease progression or responsiveness to treatment in both COPD and asthma.

Understanding the functional consequences of persistent inflammation and the ensuing structural damage/remodelling of airway and lung structure is important, difficult, and beyond the scope of this mini-review; for a succinct summary the reader is referred to an excellent article on the subject¹³ and another which outlines the functional distinctions between the centrilobular and panlobular forms of emphysema.³²

The hypersecretion of mucus which characterises chronic bronchitis has traditionally been considered to be irrelevant to the accelerated rate of decline in forced expiratory volume in one second (FEV₁) and to the disability of COPD.^{30,31} However, even the role of this apparently innocuous feature of chronic bronchitis has recently been questioned as two relatively recent studies have reported that sputum volume is associated with an accelerated decline in FEV₁, increased hospital admission, and increased mortality.^{32,33} This is in addition to the undoubted detrimental effects of mucus on the stability of small airways in COPD.⁴⁷

Inflammation appears to be present throughout the bronchial tree and respiratory portion of the lung in COPD. Similarly, there is widespread inflammation in asthma and tissue eosinophilia has recently been reported even in the alveolar walls.¹¹ The involvement of activated lymphocytes seems to be a common theme in both conditions yet the profound tissue eosinophilia of asthma does not appear in COPD. The predominant lymphocyte subsets in COPD and asthma appear to be distinct – that is, CD8+ and CD4+ cells, respectively (see table 1). Whilst there is consequent tissue destruction and remodelling in the periphery in COPD, there seems to be a contrasting trend towards involvement of relatively large proximal airways in asthma, particularly in respect of thickening of the reticular basement membrane and enlargement of the mass of bronchial smooth muscle – changes which do not occur in the large airways in COPD. The airflow limitation of COPD has two major recognised components: (1) increased resistance to airflow due mainly to the inflammatory and structural changes described in small airways and (2) loss of lung elastic recoil due to inflammation and alveolar wall destruction. It has been suggested that, when emphysema is mild to moderate, small airway lesions assume overriding importance, but if emphysema is "severe" it then dominates the contribution to decreased lung function.⁵³ Interestingly, a report by Hogg and co-workers found little relationship between macroscopic emphysema, severity score and FEV₁ and concluded that microscopic emphysema and small airway lesions were probably most responsible⁵⁴ for the deficit in lung function; this conclusion has received lively debate.⁵⁵

As many life long smokers do not succumb to emphysema, constitutional factors are also likely to be important. Genetic deficiency of alpha₁-antitrypsin is well documented and smoking in this group clearly advances the onset of emphysema and accelerates its subsequent progression. Other genetic factors such as variation in cellular response to cytotoxicity, phagocytosis, and enzyme release may be important determinants of susceptibility to cigarette smoke.⁵⁶ More recently O'Shaughnessy and colleagues¹⁰ have suggested that airway (and lung) susceptibility to the effects of cigarette smoke is likely to be greater in those individuals who already have a genetically determined low CD4:CD8+ cell ratio in their peripheral blood.⁵⁷ This is a novel explanation as to why only about 20% of smokers might succumb to its deleterious effects; however, the hypothesis requires testing and epidemiological proof.

Long term studies (soon to be reported) of the use of inhaled corticosteroids in COPD are currently in progress to test the hypothesis that airways inflammation bears a relationship with the rate of decline in FEV₁; if the relationship is a direct one then there should be a slowing of the rate of decline following attenuation of the inflammatory reaction. We await these results with interest.

The author wishes to thank Miss Leone Oscar for her help in the preparation of the manuscript.

1. Siatakas N, P. Pridé NB, Pavlota P, Gibson J, Howard B. Optimal assessment and management of chronic obstructive pulmonary disease. *COPD Eur Respir J* 1995;8:1398-420.
2. American Thoracic Society Medical Section of the American Lung Association. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;152:1077-120.
3. Summary and recommendations of a Workshop on the investigative use of fiberoptic bronchoscopy and bronchoalveolar lavage in asthmatics. *Am Rev Respir Dis* 1985;132:180-2.
4. Medical Research Council. Definition and classification of chronic bronchitis for clinical and epidemiological purposes. A report to the Medical Research Council by their Committee on the etiology of chronic bronchitis. *Lancet* 1963;ii:775-80.
5. Thurlbeck WM. Aspects of chronic airflow obstruction. *Chest* 1977;72:341-9.
6. Fletcher CM, Pridé MB. Definition of emphysema, chronic bronchitis, asthma and airflow obstruction: twenty-five years on from the CIBRA symposium. *Thorax* 1984;39:81-5.
7. Buist S, Ghezzi H, Anthonisen NR, Cherniak RK, Ducos S, Macklin PT, et al. Relationship between the single breath N₂ test and age, sex and smoking habits in three North American cities. *Am Rev Respir Dis* 1979;120:305-18.
8. Buist AS. Current status of small airways disease. *Chest* 1984;86:100-5.
9. Snider GL, Kleinerman J, Thurlbeck WM. The definition of emphysema. Report of a National Heart and Blood Institute, division of lung diseases, Workshop. *Am Rev Respir Dis* 1985;132:182-5.
10. O'Shaughnessy TC, Ansari TW, Barnes NC, Jeffery PK. Inflammation in bronchial biopsies of subjects with chronic bronchitis: inverse relationship of CD8+ T lymphocytes with FEV₁. *Am J Respir Crit Care Med* 1997;155:552-7.
11. Jeffery PK. Pathology of asthma. *Br Med Bull* 1992;48:23-39.
12. Jeffery PK. Tobacco smoke-induced lung disease. In: Cohen RD, Lewis B, Alberti KGMM, Denman AM, eds. *The metabolic and molecular basis of acquired disease*. London: Baillière Tindall, 1990:466-95.
13. Saetta M, Finkelstein R, Cosio MG. Morphological and cellular basis for airflow limitation in smokers. *Eur Respir J* 1994;7:1505-15.
14. Jeffery PK. Cigarette smoke-induced damage of airway mucosa. In: Chretien J, Dusser D, eds. *Environmental impact on the airways*. New York: Marcel Dekker, 1996:299-354.
15. Toremalm NH. The daily amount of tracheobronchial secretions in man: a method for continuous tracheal aspiration in laryngectomized and tracheostomized patients. *Acta Otolaryngol* 1960;158:43-53.
16. Lopez-Vidnerio MT, Reid L. Bronchial mucus in asthma. In: Weiss EB, Segal MS, Stein M, eds. *Bronchial asthma: mechanisms and therapeutics*. Boston: Little Brown, 1985:213-35.
17. Coles SJ, Bhaskar KR, O'Sullivan BD, Neill KH, Reid LM. Airway mucus: composition and regulation of its secretion by neuropeptides in vitro. In: *Mucus and mucosa*. Ciba Foundation Symposium 109. London: Pitman Medical, 1984:40-60.
18. Reid L. Pathology of chronic bronchitis. *Lancet* 1954;ii:275-9.
19. Dunnill MS, Massarella GR, Anderson JA. A comparison of the quantitative anatomy of the bronchi in normal subjects, in status asthmaticus, in chronic bronchitis, and in emphysema. *Thorax* 1969;24:170-9.
20. Cosio MG, Hale KA, Niewoehner DE. Morphologic and morphometric effects of prolonged cigarette smoking on the small airways. *Am Rev Respir Dis* 1980;122:265-71.
21. Ebert RV, Terracio MJ. The bronchiolar epithelium in cigarette smokers: observations with the scanning electron microscope. *Am Rev Respir Dis* 1975;111:4-11.
22. Glynn AA, Michaels L. Bronchial biopsy in chronic bronchitis and asthma. *Thorax* 1960;15:142-53.
23. Wright RR, Stuart CM. Chronic bronchitis with emphysema: a pathological study of the bronchi. *Medicina Thoracica* 1965;22:210.
24. Kleinerman J, Boren HG. Morphologic basis of chronic obstructive lung disease. In: Baum GL, ed. *Textbook of pulmonary disease*. Boston: Little Brown, 1974:571.
25. Ailsby RL, Ghadially FN. Atypical cells in human bronchial mucosa. *J Pathol* 1973;109:75-7.
26. Chang SC. Microscopic properties of whole mounts and sections of human bronchial epithelium of smokers and non-smokers. *Cancer (Phila)* 1957;10:1246-62.
27. Wanner A. Clinical aspects of mucociliary transport. *Am Rev Respir Dis* 1977;116:73-125.
28. Misokovitch G, Appel J, Szule J. Ultrastructural changes of ciliated columnar epithelium and goblet cells in chronic bronchitis biopsy material. *Acta Morphol Acad Sci Hung* 1974;22:91-103.
29. Horsfield K. The structure of the tracheobronchial tree. In: Scadding JG, Cumming G, Thurlbeck WM, eds. *The structure of the tracheobronchial tree*. London: William Heinemann, 1981:54-70.
30. Nemery B, Moavero NE, Brasseur L, Stanesco DC. Significance of small airways test in middle-aged smokers. *Am Rev Respir Dis* 1981;124:232-5.
31. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med* 1968;278:1353-60.

29. Kien EK, Casperberg M, Mertens I, Lauweryns JM, de Waele K. Tissue and airway impedance of excised normal, senile, and emphysematous lungs. *Am J Physiol* 1992;263:533-537.
30. Nieuwenner DE, Kienerman J, Rode D. Pathologic changes in the peripheral airways of young cigarette smokers. *N Engl J Med* 1971;291:755-5.
31. Reynolds HJ. Bronchoalveolar lavage. *Am Rev Respir Dis* 1987;135:250-63.
32. Mitchell RS, Stanford RE, Johnson JM, Silvers GW, Dart G, George MS. The morphologic features of the bronchioles and alveoli in chronic airway obstruction: a clinicopathologic study. *Am Rev Respir Dis* 1976;114:137-45.
33. Hale KA, Ewing SL, Gosnell BA, Nieuwenner DE. Lung disease in long-term cigarette smokers with and without chronic air-flow obstruction. *Am Rev Respir Dis* 1984;130:716-21.
34. Bignon J, Khoury F, Evan P, Andre J, Brouet G. Morphometric study in chronic obstructive broncho-pulmonary disease. *Am Rev Respir Dis* 1969;99:669-75.
35. Saetta M, Ghezzi H, Wong Dong Kim, King M, Angus GE, Wang N-S, Cosio MG. Loss of alveolar attachments in smokers. A morphometric correlate of lung function impairment. *Am Rev Respir Dis* 1985;132:894-900.
36. Linhartova A, Anderson AE Jr, Foraker AG. Further observations on lumenal deformity and stenosis of non respiratory bronchioles in pulmonary emphysema. *Thorax* 1977;32:50-3.
37. Anderson AE, Foraker AG. Relative dimensions of bronchioles and parenchymal spaces in lungs from normal subjects and emphysematous patients. *Am J Med* 1962;32:218-26.
38. Jeffery PK, Reid L. New observations of rat airway epithelium: a quantitative electron microscopic study. *J Anat* 1975;120:295-320.
39. Jeffery PK. Structural, immunologic, and neural elements of the normal human airway wall. In: Busse WW, Holgate ST, eds. *Asthma and rhinitis*. Oxford: Blackwell Scientific Publications, 1993:80-106.
40. Gil J, Weibel E. Extracellular lining of bronchioles after perfusion-fixation of rat lungs for electron microscopy. *Anat Rec* 1971;169:185-200.
41. Mooren HWD, Kramps JA, Franken C, Meijer CJLM, Dijkman JA. Localisation of a low-molecular weight bronchial protease inhibitor in the peripheral human lung. *Thorax* 1983;38:180-3.
42. Kramps JA, Franken C, Dijkman JA. ELISA for quantitative measurement of low-molecular-weight bronchial protease inhibitor in human sputum. *Am Rev Respir Dis* 1984;129:959-63.
43. Ebert RV, Hanks PB. Mucus secretion by the epithelium of the bronchioles of cigarette smokers. *Br J Dis Chest* 1981;75:277-82.
44. Macklem PT, Proctor DF, Hogg JC. The stability of peripheral airways. *Resp Physiol* 1970;8:191-203.
45. Gillooly M, Lamb D. Microscopic emphysema in relation to age and smoking habit. *Thorax* 1993;48:491-5.
46. Lamb D, McLean A, Gillooly M, Warren PM, Gould GA, MacNee W. Relation between distal airspace size, bronchiolar attachments, and lung function. *Thorax* 1993;48:1012-7.
47. Lang MR, Fiaux GW, Gillooly M, Stewart JA, Hulmes DJS, Lamb D. Collagen content of alveolar wall tissue in emphysematous and non-emphysematous lungs. *Thorax* 1994;49:319-26.
48. Enksson S. Pulmonary emphysema and alpha 1-antitrypsin deficiency. *Acta Med Scand* 1964;175:197-205.
49. Kim WD, Eidelman DH, Izquierdo JL, Ghezzi H, Saetta MP, Cosio MG. Centrilobular and panlobular emphysema in smokers. Two distinct morphologic and functional entities. *Am Rev Respir Dis* 1991;144:1385-90.
50. Auerbach O, Hammond EC, Garfinkel L, Benante C. Relation of smoking and age to emphysema. *N Engl J Med* 1972;286:853-8.
51. Gadek JE, Fells GA, Crystal RG. Cigarette smoking induces functional antiprotease deficiency in the lower respiratory tract of humans. *Science* 1979;206:1315-6.
52. Cantin A, Crystal RG. Oxidants, antioxidants and the pathogenesis of emphysema. *Eur J Respir Dis* 1985;66(Suppl 139):7-17.
53. Kimbel P. Proteolytic damage and emphysema pathogenesis. In: Petty TL, ed. *Chronic obstructive pulmonary disease*. Vol 28. New York: Dekker, 1985:105-28.
54. MacNee W. Pathophysiology of cor pulmonale chronicum in chronic obstructive pulmonary disease (COPD). Part One. *Am J Respir Crit Care Med* 1994;150:333-52.
55. Wright JL, Hobson JE, Wiggs B, Pare PD, Hogg JC. Airway inflammation and peribronchiolar attachments in the lungs of nonsmokers, current and ex-smokers. *Lung* 1988;166:277-86.
56. Snider GL. Chronic obstructive pulmonary disease - a continuing challenge. *Am Rev Respir Dis* 1986;133:942-4.
57. Thurlbeck WM. Chronic airflow obstruction. Correlation of structure and function. In: Petty TL, ed. *Chronic obstructive pulmonary disease*. New York: Dekker, 1985:129.
58. MacNee W, Selby C. New perspectives on basic mechanisms in lung disease: 2. Neutrophil traffic in the lungs: role of haemodynamics, cell adhesion and deformability. *Thorax* 1993;48:79-88.
59. MacNee W, Wiggs B, Belzberg AS, Hogg JC. The effect of cigarette smoking on neutrophil kinetics in human lungs. *N Engl J Med* 1989;321:924-8.
60. Drost EM, Selby C, Lannan S, Lowe GDO, MacNee W. Changes in neutrophil deformability following in vitro exposure: mechanisms and protection. *Am J Respir Crit Care Med* 1992;146:257-65.
61. Finkstein R, Fraser RS, Ghezzi H, Cosio MG. Alveolar inflammation and its relation to emphysema in smokers. *Am J Respir Crit Care Med* 1995;152:1699-702.
62. Jeffery PK, Wardlaw AJ, Nelson FC, Collins JV, Kay AB. Bronchial biopsies in asthma: an ultrastructural quantitation study and correlation with hyperreactivity. *Am Rev Respir Dis* 1989;140:1745-53.
63. Azzawi M, Bradley B, Jeffery PK, Frew AJ, Wardlaw AJ, Assoufi B, et al. Identification of activated T lymphocytes and eosinophils in bronchial biopsies in stable atopic asthma. *Am Rev Respir Dis* 1990;142:1407-13.
64. Bradley BL, Azzawi M, Jacobson M, Assoufi B, Collins JV, Irani A-MA, et al. Eosinophils, T-lymphocytes, mast cells, neutrophils and macrophages in bronchial biopsies from atopic asthmatics: comparison with atopic non-asthma and relationship to bronchial hyperresponsiveness. *J Allergy Clin Immunol* 1991;88:601-74.
65. Robinson DS, Hamid Q, Ying S, Tzicopoulos A, Barkan J, Bentley AM, et al. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med* 1992;326:298-304.
66. Robinson DS, Tzicopoulos A, Meng Q, Durham S, Kay AB, Hamid Q. Increased interleukin-10 messenger RNA expression in atopic allergy and asthma. *Am J Respir Cell Mol Biol* 1996;14:113-7.
67. Humbert M, Durham SR, Ying S, Kimmitt P, Barkan J, Assoufi B, et al. IL-4 and IL-5 mRNA and protein in bronchial biopsies from atopic and non-atopic asthma. Evidence against "intrinsic" asthma being a distinct immunopathological entity. *Am J Respir Crit Care Med* 1996;154:1497-1504.
68. Djukanovic R, Roche WR, Wilson JW, Beasley CRW, Twentyman P, Howarth PH, et al. Mucosal inflammation in asthma. *Am Rev Respir Dis* 1990;142:434-57.
69. Lacoste JY, Bousquet J, Chanez P, Vanvyve T, Simony-Lafontaine J, Lequeu N, et al. Eosinophilic and neutrophilic inflammation in asthma, chronic bronchitis, and chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 1993;92:537-48.
70. Ollerenshaw SL, Woolcock AJ. Characteristics of the inflammation in biopsies from large airways of subjects with asthma and subjects with chronic airflow limitation. *Am Rev Respir Dis* 1992;145:922-7.
71. Saetta M, Di Stefano A, Maestrelli P, Ferrarasso A, Drigo R, Potena A, et al. Activated T-lymphocytes and macrophages in bronchial mucosa of subjects with chronic bronchitis. *Am Rev Respir Dis* 1993;147:301-6.
72. Vignola AM, Campbell AM, Chanez P, Bousquet J, Paul-Lacoste P, Michel F-B, et al. HLA-DR and ICAM-1 expression on bronchial epithelial cells in asthma and chronic bronchitis. *Am Rev Respir Dis* 1993;148:689-94.
73. Di Stefano A, Maestrelli P, Roggeri A, Turato G, Calabro S, Potena A, et al. Upregulation of adhesion molecules in the bronchial mucosa of subjects with chronic obstructive bronchitis. *Am J Respir Crit Care Med* 1994;149:803-10.
74. Saetta M, Di Stefano A, Maestrelli P, Turato G, Ruggieri P, Calcagni P, et al. Airway eosinophilia in chronic bronchitis during exacerbations. *Am J Respir Crit Care Med* 1994;150:1646-52.
75. Thompson AB, Daughton D, Robbins RA, Ghafouri MA, Oehlerting M, Reinard SI. Intraluminal airway inflammation in chronic bronchitis. Characterization and correlation with clinical parameters. *Am Rev Respir Dis* 1989;140:1527-37.
76. Lacoste J-Y, Bousquet J, Chanez P, Van Vyve T, Simony-Lafontaine J, Lequeu N, et al. Eosinophilic and neutrophilic inflammation in asthma, chronic bronchitis, and chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 1993;92:537-48.
77. Fletcher CM. Chronic bronchitis and decline in pulmonary function with some suggestions on terminology. In: Cummings G, Bonsignore G, eds. *Smoking and the lung*. Vol 17. New York: Plenum, 1984:397-420.
78. Peto R, Speitzer FE, Cochrane AL, Moore F, Fletcher CM, Tinker CM, et al. The relevance in adults of airflow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease. *Am Rev Respir Dis* 1983;128:491-500.
79. Prescott E, Lange P, Vestbo J. Chronic mucus hypersecretion in COPD and death from pulmonary infection. *Eur Respir J* 1995;8:1333-8.
80. Vestbo J, Prescott E, Lange P. Association of chronic mucus hypersecretion with FEV₁ decline and chronic obstructive pulmonary disease morbidity. *Am J Respir Crit Care Med* 1996;153:1530-5.
81. Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. *Am J Respir Crit Care Med* 1996;154:1505-10.
82. Hogg JC, Wright JL, Wiggs BR, Coxson HO, Saez AO, Pare PD. Lung structure and function in cigarette smokers. *Thorax* 1994;49:473-8.
83. Thurlbeck WM. Lung structure and function in cigarette smokers. *Thorax* 1994;49:1270-9.
84. Hopkin JM, Tomlinson CS, Jenkins RM. Variations in response to cytotoxicity of cigarette smoke. *BMJ* 1981;283:1200-11.
85. Amadori A, Zamarchi R, De Silvestro G, Forza G, Cavatton G, Antonio Danieli G, et al. Genetic control of the CD8/CD4 T-cell ratio in humans. *Nature Medicine* 1995;1:1279-83.
86. Jeffery PK. Comparative morphology of the airways in asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994;150:50-13.

LONG-TERM TREATMENT WITH INHALED BUDESONIDE IN PERSONS WITH MILD CHRONIC OBSTRUCTIVE PULMONARY DISEASE WHO CONTINUE SMOKING

ROMAIN A. PAUWELS, M.D., CLAES-GÖRAN LÖFDAHL, M.D., LAURI A. LAITINEN, M.D., JAN P. SCHOUTEN, Ph.D.,
DIRKJE S. POSTMA, M.D., NEIL B. PRIDE, M.D., AND STEFAN V. ÖHLSSON, Ph.D.,
FOR THE EUROPEAN RESPIRATORY SOCIETY STUDY ON CHRONIC OBSTRUCTIVE PULMONARY DISEASE*

ABSTRACT

Background and Methods Although patients with chronic obstructive pulmonary disease (COPD) should stop smoking, some do not. In a double-blind, placebo-controlled study, we evaluated the effect of the inhaled glucocorticoid budesonide in subjects with mild COPD who continued smoking. After a six-month run-in period, we randomly assigned 1277 subjects (mean age, 52 years; mean forced expiratory volume in one second (FEV₁), 77 percent of the predicted value; 73 percent men) to twice-daily treatment with 400 µg of budesonide or placebo, inhaled from a dry-powder inhaler, for three years.

Results Of the 1277 subjects, 912 (71 percent) completed the study. Among these subjects, the median decline in the FEV₁ after the use of a bronchodilator over the three-year period was 140 ml in the budesonide group and 180 ml in the placebo group (P=0.05), or 4.3 percent and 5.3 percent of the predicted value, respectively. During the first six months of the study, the FEV₁ improved at the rate of 17 ml per year in the budesonide group, as compared with a decline of 81 ml per year in the placebo group (P<0.001). From nine months to the end of treatment, the FEV₁ declined at similar rates in the two groups (P=0.39). Ten percent of the subjects in the budesonide group and 4 percent of those in the placebo group had skin bruising (P<0.001). Newly diagnosed hypertension, bone fractures, postcapsular cataracts, myopathy, and diabetes occurred in less than 5 percent of the subjects, and the diagnoses were equally distributed between the groups.

Conclusions In persons with mild COPD who continue smoking, the use of inhaled budesonide is associated with a small one-time improvement in lung function but does not appreciably affect the long-term progressive decline. (N Engl J Med 1999;340:1948-53.)
©1999, Massachusetts Medical Society.

CHRONIC obstructive pulmonary disease (COPD) is characterized by a progressive and largely irreversible limitation of airflow. Cigarette smoking is the principal risk factor, and smoking cessation has been shown to decrease the rate of decline in lung function,¹ but the success of smoking-cessation programs is limited.²

The decline in lung function in patients with COPD is related to the presence of inflammatory

changes in the airways and lung parenchyma.³ Airway inflammation in COPD differs from such inflammation in asthma.⁴ Inhaled glucocorticoids are successfully used in asthma.⁵ Some studies have shown an effect of inhaled glucocorticoids on airway inflammation in COPD.⁶⁻⁹ In this study, we tested the hypothesis that regular treatment with the inhaled glucocorticoid budesonide would reduce the decline in lung function in patients with mild COPD who continued smoking.¹⁰

METHODS

Study Design

The study was a parallel-group, double-blind, placebo-controlled, randomized, multicenter study. Thirty-nine study centers in nine European countries (Belgium, Denmark, Finland, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) participated. Approval from regulatory and ethics committees was obtained at all centers. All subjects gave written informed consent.

The study started with a run-in phase consisting of a three-month smoking-cessation program. All subjects received extensive information about the health hazards of smoking and a starting package of nicotine gum. More extensive smoking-cessation programs were encouraged. In subjects who did not stop smoking, this phase was followed by a three-month period during which compliance with inhaled medication was assessed with the use of a placebo-containing dry-powder inhaler with a hidden mechanical counter. Subjects who continued smoking and were at least 75 percent compliant with the recommended treatment regimen were randomly assigned to twice-daily treatment with either 400 µg of budesonide (Pulmicort, Astra, Stockholm, Sweden) or placebo from a dry-powder inhaler (Turbohaler, Astra) for three years. The primary outcome variable was the change over time in forced expiratory volume in one second (FEV₁) after use of a bronchodilator.

Subjects

Persons 30 to 65 years of age were eligible if they were currently smoking at least five cigarettes per day and had smoked cigarettes for at least 10 years or had a smoking history of at least 5 pack-

From the Department of Respiratory Diseases, University Hospital, Ghent, Belgium (R.A.P.); the Department of Respiratory Medicine, University Hospital, Lund, Sweden (C.-G.L.); the Department of Medicine, University Central Hospital, Helsinki, Finland (L.A.L.); the Department of Epidemiology and Statistics, University of Groningen, Groningen, the Netherlands (J.P.S.); the Division of Respiratory Disease, University Hospital, Groningen, the Netherlands (D.S.P.); the Respiratory Division, Imperial College School of Medicine, Hammersmith Hospital, London (N.B.P.); and Clinical Research and Development, Astra Draco, Lund, Sweden (S.V.O.). Address reprint requests to Dr. Pauwels at the Department of Respiratory Diseases, University Hospital, De Pintelaan 185, B9000 Ghent, Belgium, or at romain.pauwels@rug.ac.be.

*The other participants in the study are listed in the Appendix.

years. The FEV₁ after the use of a bronchodilator had to be between 50 percent and 100 percent of the predicted normal value,¹¹ and the ratio of prebronchodilator FEV₁ to slow vital capacity had to be less than 70 percent. The increase in FEV₁ after the inhalation of 1 mg of terbutaline from a dry-powder inhaler had to be less than 10 percent of the predicted normal value. The change in FEV₁ between the end of the first three-month period of the run-in phase and the end of the second had to be less than 15 percent. Subjects with a history of asthma, allergic rhinitis, or allergic eczema and those who had used oral glucocorticoids for more than four weeks during the preceding six months were excluded. The use of inhaled glucocorticoids other than the study medication, beta-blockers, cromones, or long-acting inhaled β_2 -adrenergic agonists was not allowed.

Outcome Measures

Clinic Visits

The subjects were seen at the clinics every three months for spirometry and evaluation of smoking habits, compliance with medication, and safety-related variables. At selected centers, bone density was measured before treatment and after 6, 12, 24, and 36 months. Spine radiographs were obtained before and at the end of treatment.

Spirometry

Each center was supplied with a dry rolling-seal spirometer (model SMI III, Spirometrics, Auburn, Me.). The criteria of the American Thoracic Society¹² were used to determine FEV₁. All technicians attended an initial training session about the spirometer and the techniques to be used. Thereafter, regular visits were made by a monitor to check the calibration of the spirometer and to monitor the technique.

Spirometry was performed with the subject seated and wearing a nose clip. At recruitment and at the end of the study, slow vital capacity and FEV₁ were measured after at least 6 hours without inhaled bronchodilators and after 24 hours without oral bronchodilators. Three technically adequate and two reproducible maneuvers were required for the measurement of slow vital capacity and FEV₁. The largest values measured for slow vital capacity and FEV₁ were accepted, provided the second largest measurement was within 0.1 liter or 5 percent of the largest measurement. At all clinic visits, FEV₁ was obtained 15 minutes after the inhalation of 1 mg of terbutaline. Values were corrected for body temperature, ambient pressure, and water saturation and compared with the reference values of the European Community for Coal and Steel.¹¹

Safety Studies and Serum Analysis

At each visit, subjects were specifically asked whether they had received a diagnosis of glucocorticoid-related diseases or conditions such as hypertension, bone fractures, posterior subcapsular cataracts, myopathy, or diabetes in the preceding period. The number of skin bruises larger than 50 mm in diameter on the volar side of the forearms was noted. All other adverse events were recorded. Serious adverse events were those that were judged by the investigators to constitute a hazard or handicap to the subject.

Lateral thoracic and lumbar spinal radiographs were obtained with standard values for target-to-film distance and centering. The films were sent to a central evaluator who was unaware of the treatment received and were analyzed according to a standardized computerized protocol. The presence or absence of vertebral fractures at base line was determined by comparing each subject's base-line vertebral height ratio with reference values. A new fracture was defined as a reduction of at least 20 percent, with an absolute decrease of at least 4 mm, in the height of any vertebral body.¹³

We measured the bone mineral density of the lumbar spine (L2 to L4), the femoral neck, Ward's triangle, and the trochanter by dual-energy x-ray absorptiometry with a densitometer (model QDR-1000, Hologic, Waltham, Mass., or model DPX-L, Lunar, Madison, Wis.). The quality of the instruments was assessed before

and then monthly during the study by an external organization (Bona Fide, Madison, Wis.).

At randomization a blood sample was taken to test for IgE antibodies (Phadiatop, Pharmacia & Upjohn, Uppsala, Sweden).

Statistical Analysis

The sample size was based on an estimated standard deviation of the mean slope of the FEV₁ of 100 ml per year according to a previous study,¹⁴ a withdrawal rate of 40 percent, and a power of 80 percent to detect a difference in treatment response of 20 ml per year. Data on the randomized subjects were analyzed on an intention-to-treat basis. Student's *t*-test was used to compare treatment groups with respect to normally distributed variables, and the Wilcoxon rank-sum test was used for other variables. The χ^2 test was used to compare categorical variables. Differences were assessed with two-sided tests, with an alpha level of 0.05.

Several models were used to assess the serial changes in the variables of interest in the longitudinal data. First, the change in the variables over time was examined graphically. Unweighted and weighted individual regression lines of the variable of interest against time were used to estimate the slopes for each subject. The weighted regression lines were estimated by linear-mixed-effects modeling,¹⁵⁻¹⁷ with intercept and time in the model as both fixed and random effects. The slopes were calculated for various periods with stratification according to confounders, effect modifiers, or both, and were compared between treatment groups.

Piecewise linear regression analysis of FEV₁ against time within the budesonide group with a linear-mixed-effects model showed a best fit with one breakpoint after three or six months of treatment and fitted significantly better than a model that assumed linearity over the whole study period. The study period was therefore partitioned into two periods. The best fit was determined with the likelihood-ratio test for nested models or with Akaike's information criterion statistic.¹⁸

The data are presented either as absolute changes for all subjects who were in the study at a certain time or as unweighted slopes on the intention-to-treat population. These data are presented as median values, since their distribution was not normal.

RESULTS

From January 1992 to July 1993, 2157 potential subjects were recruited at the participating centers. Of these, 462 were found to be ineligible, and the remaining 1695 were enrolled in the smoking-cessation program, during which 169 (10 percent) stopped smoking. Of the remaining 1526 subjects, 1277 (84 percent) were compliant with the inhaled medication, continued smoking, and were randomly assigned to treatment (643 to placebo and 634 to budesonide). Nine hundred twelve subjects (71 percent) remained in the study for three years. During the study, 198 subjects were withdrawn because of non-compliance with the study procedures, 132 were withdrawn because of adverse events, and 35 were lost to follow-up, resulting in 176 withdrawals from the budesonide group and 189 from the placebo group. The reasons for withdrawal were similar in the two groups.

The base-line characteristics of the subjects in the two groups were similar (Table 1). The mean age was 52 years; 354 (27 percent) were women. The majority had been heavy cigarette smokers for many years and had mild, poorly reversible airflow limitation. The subjects had decreased their cigarette consumption during the six months before randomization (to a mean of 18.8 and 17.3 cigarettes per day, respec-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 1277 SUBJECTS AT ENROLLMENT.*

CHARACTERISTIC	PLACEBO GROUP (N=643)	BUDESONIDE GROUP (N=634)
Age (yr)	52.4±7.7	52.5±7.5
Male sex (%)	72.2	73.5
Height (cm)	173±9	173±8
Weight (kg)	73.9±13.6	74.7±13.2
Prebronchodilator FEV ₁ (liters)	2.54±0.64	2.53±0.64
Prebronchodilator FEV ₁ (% of predicted)	76.9±13.2	76.8±12.4
FEV ₁ /SVC	61.7±7.0	62.2±6.8
Reversibility of FEV ₁ (% of predicted)†	2.8±3.6	2.9±3.8
Pack-years of smoking	39.2±20.1	39.4±20.1
Age when started smoking (yr)	16.4±3.8	16.8±3.9
Duration of smoking (yr)	35.9±8.2	35.8±7.8
Smoking at entry (no. of cigarettes/day)	22.4±11.1	22.0±9.8
Smoking at randomization (no. of cigarettes/day)	17.3±10.5	18.8±11.1
Positive Phadiatop test (%)‡	18.9	17.7

*Plus-minus values are means ± SD. FEV₁ denotes forced expiratory volume in one second, and SVC slow vital capacity.

†This variable was measured after the inhalation of 1 mg of terbutaline.

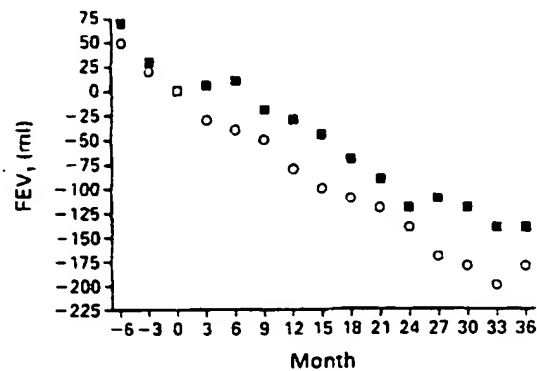
‡The Phadiatop test detects the presence in serum of IgE antibodies to a panel of common inhalant allergens.

tively, in the budesonide and placebo groups at randomization). An increasing number of subjects in both treatment groups reported quitting smoking during the treatment period. At the end of the study, approximately 10 percent of the subjects (9.1 percent of the budesonide group and 11.2 percent of the placebo group) reported not smoking during the previous six months.

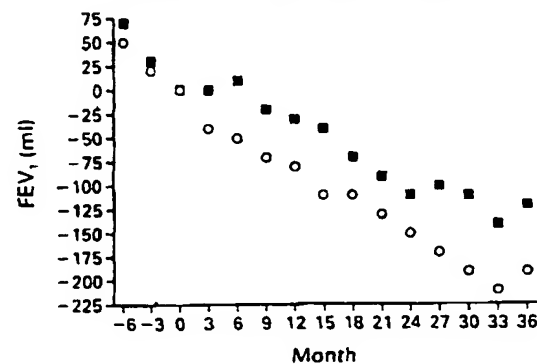
Changes in FEV₁ Values after Bronchodilator Use over Time

The changes in postbronchodilator FEV₁ over time differed between the two treatment groups (Fig. 1). The placebo group showed a linear decline in FEV₁ over time, with a slope of -65 ml per year. In the budesonide group, the FEV₁ improved over the first six months at a rate of 17 ml per year, as compared with a decline of 81 ml per year in the placebo group ($P<0.001$). However, the slopes from nine months to the end of treatment were similar in the two groups: -57 ml per year in the budesonide group and -69 ml per year in the placebo group ($P=0.39$) (Table 2). During that period, 55 percent of the subjects in the placebo group had a rapid decline in FEV₁ (more than 60 ml per year), as compared with 49 percent of the subjects in the budesonide group ($P=0.06$). In the 912 subjects who completed the study, the median decline in FEV₁ over the three-year period was 140 ml in the budesonide group and

All Subjects Treated



Subjects with ≤36 Pack-Year History



Subjects with >36 Pack-Year History

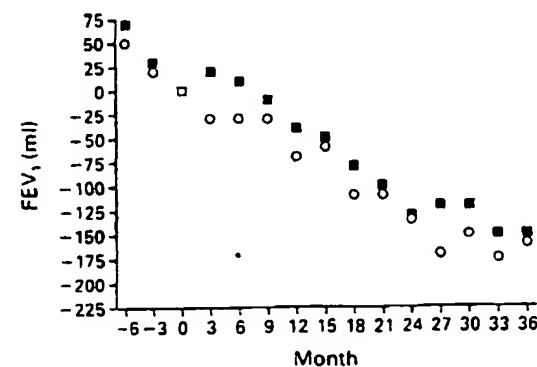


Figure 1. Median Change in Forced Expiratory Volume in One Second (FEV₁) as Compared with the Value at Randomization (Month 0) in the Placebo (○) and Budesonide (■) Groups.

The change is shown for all subjects treated, for subjects with a smoking history of 36 pack-years or less, and for subjects with a smoking history of more than 36 pack-years.

TABLE 2. CHANGE IN FEV₁ OVER TIME IN THE TWO TREATMENT GROUPS ACCORDING TO SMOKING HISTORY.*

SMOKING HISTORY	TREATMENT PERIOD	CHANGE IN FEV ₁ †		P VALUE
		PLACEBO	BUDESONIDE	
		ml	ml/yr	
All subjects	0-6	-81	17	<0.001
	9-36	-69	57	0.39
Subjects with ≤36 pack-yr history	0-6	-90	30	<0.001
	9-36	-71	-47	0.08
Subjects with >36 pack-yr history	0-6	-70	0	0.57
	9-36	-65	-67	0.65

*Subjects were divided into two equal groups according to their smoking history at enrollment. The median was 36 pack-years. FEV₁ denotes forced expiratory volume in one second.

†The change is shown as the median of the FEV₁ slopes (in milliliters per year) during different parts of the study.

TABLE 3. SERIOUS ADVERSE EVENTS, DISCONTINUATIONS DUE TO ADVERSE EVENTS, DEATHS, AND GLUCOCORTICOID-RELATED SIDE EFFECTS.

EVENT*	SUBJECTS WITH AT LEAST ONE ADVERSE EVENT		P VALUE
	PLACEBO GROUP	BUDESONIDE GROUP	
Serious adverse event — no.	161	177	0.37
Neoplasm	25	31	
Cardiovascular disorder	32	28	
Gastrointestinal disorder	15	17	
Respiratory disorder	14	17	
Musculoskeletal disorder	16	14	
Discontinuation due to adverse events — no.	62	70	0.51
Bronchial carcinoma	10	7	
Myocardial infarction	5	5	
Oropharyngeal candidiasis	0	8	
Coughing	4	3	
Urinary-bladder carcinoma	4	3	
Deaths — no.†	10	8	0.64
Glucocorticoid-related side effects			
Oropharyngeal candidiasis — no.	10	31	<0.001
Pharyngeal irritation or hoarseness — no.	28	46	
New lumbar fractures			0.50
No. of subjects	3	5	
No. of fractures	3	8	
Skin bruises — no. of subjects (%)	27 (4)	63 (10)	<0.001
Cumulative no. of bruises	42	364	

*The five most frequent categories of serious adverse events and the five most frequent adverse events leading to discontinuation are listed. A serious adverse event was defined as an adverse event that was judged by the investigators to constitute a hazard or a handicap to the subject.

†The causes of death in the placebo group were bronchial carcinoma (3 subjects), sudden cardiac arrest (2), trauma (2), myocardial infarction (1), pulmonary embolism (1), and exacerbation of COPD (1). The causes of death in the budesonide group were bronchial carcinoma (3), myocardial infarction (2), sudden cardiac arrest (1), ruptured aortic aneurysm (1), and gastric carcinoma (1).

180 ml in the placebo group ($P=0.05$), or 4.3 percent and 5.3 percent of their respective predicted values ($P=0.04$).¹¹

Budesonide had a more beneficial effect in subjects who had smoked less (Fig. 1). Subjects with a history of smoking that was at or below the median of 36 pack-years at enrollment had a decrease in FEV₁ of 190 ml during placebo treatment and of 120 ml during budesonide treatment ($P<0.001$). The loss of FEV₁ in three years among subjects with more than 36 pack-years of smoking was 160 ml during placebo treatment and 150 ml during budesonide treatment ($P=0.57$). Analysis of FEV₁ slopes indicated that age, sex, base-line FEV₁, the presence or absence of serum IgE antibodies, and reversibility of airflow limitation had no significant effects on the outcome of treatment.

Similar percentages of subjects stopped smoking in both treatment groups; thus, stopping smoking did not explain the difference in the change in FEV₁ between the groups. When we compared the change in FEV₁ between the subjects who continued smoking at the same rate and those who either decreased their consumption by more than five cigarettes per day or stopped completely, we found a nonsignificant trend toward a beneficial effect in addition to the effect of budesonide.

Side Effects and Safety

More subjects in the budesonide group had skin bruising (Table 3). In total, 10 percent of subjects in the budesonide group and 4 percent of those in the placebo group had bruises during the study ($P<0.001$). The highest prevalence of bruises at any visit was 4.9 percent in the budesonide group and 1.4 percent in the placebo group.

Bone density was measured in 194 subjects (102 in the budesonide group and 92 in the placebo group). There was no significant change over time and no significant effect of treatment on bone density, except for a small but significant difference at the femoral trochanter in favor of budesonide. The yearly decline in the bone density of the trochanter was 0.38 percent in the placebo group and 0.04 percent in the budesonide group ($P=0.02$).

Two sets of radiographs of the spine were assessed in 653 subjects, 185 women and 468 men. At randomization, 43 in the budesonide group (13.4 percent) and 38 in the placebo group (11.5 percent) had at least one vertebral fracture. During the study, new fractures were unusual (three in the placebo group and eight in the budesonide group) and were similarly distributed ($P=0.50$).

Newly diagnosed hypertension, bone fractures, postcapsular cataracts, myopathy, and diabetes occurred in less than 5 percent of the subjects and were equally distributed between the groups (data not shown).

Serious Adverse Events

Serious adverse events were equally distributed between the groups (Table 3). Seventy patients in the budesonide group were withdrawn from the study, as compared with 62 in the placebo group ($P=0.51$). More subjects in the budesonide group withdrew from the study because of nonserious adverse events (35, vs. 23 in the placebo group), mainly oropharyngeal candidiasis (8 in the budesonide group and none in the placebo group) and local irritation of the throat or dysphonia (8 in the budesonide group and 2 in the placebo group).

DISCUSSION

Patients with COPD must always be advised and encouraged to stop smoking, and they should be offered treatment programs to facilitate smoking cessation. Nonetheless, some patients continue to smoke. In such patients with mild COPD, we found that the use of inhaled budesonide was associated with a small, one-time improvement in the FEV₁ after bronchodilator use, but that it did not appreciably affect the long-term progressive decline in lung function.

In the placebo group, the postbronchodilator FEV₁ declined by a median of 180 ml over a period of three years, the median slope being -65 ml per year. In the budesonide group, the median decrease in FEV₁ over the three years was 140 ml. The benefit of budesonide was limited to the initial six months of treatment. The beneficial effect of budesonide was greater in subjects with a history of fewer pack-years of smoking.

We studied subjects with mild COPD (mean FEV₁, 77 percent of the predicted value at base line) and a history of moderate-to-heavy cigarette smoking. These characteristics are similar to those of the patients in the Lung Health Study.¹ We attempted to exclude subjects with asthma by eliminating those with a history of asthma or any other atopic disease or with reversible airflow limitation. The presence or absence of IgE antibodies or the degree of reversibility of the airflow limitation did not influence the effect of budesonide. The decline in FEV₁ in the placebo group corresponds with findings in other long-term follow-up studies of COPD.^{1,19,20}

Most studies of glucocorticoid treatment in patients with COPD have examined short-term effects on airflow limitation.^{8,14,21-29} Results have been variable, but several studies have found an increase in FEV₁ after treatment with oral or inhaled glucocorticoids.^{21,22,25,29} The change in FEV₁ during the first months of our study is in line with these findings. Few studies have investigated the effect of glucocorticoid treatment on the long-term change in FEV₁ in patients with COPD. Two retrospective studies suggested that daily treatment with prednisolone might slow the progressive decline in FEV₁.^{30,31} In a small group of patients with COPD who had previously

been treated with bronchodilators, Dompeling et al.^{33,32} observed that daily treatment with 800 µg of beclomethasone was associated with an increase in prebronchodilator FEV₁ during the first 6 months of treatment, followed by a decline during the remaining 18 months of the treatment period. In a two-year controlled study in a small group of patients with COPD, Renkema et al.³⁴ did not find a significant effect of treatment with budesonide (800 µg twice daily alone or in combination with 5 mg of prednisolone daily) on the decline in FEV₁.

We also examined the side effects of inhaled glucocorticoids in a group of middle-aged smokers. An increased prevalence of skin bruising in patients treated with high doses of inhaled glucocorticoids has been reported in cross-sectional studies.^{33,34} In our study, the budesonide group had an overall incidence of skin bruising of 10 percent, as compared with 4 percent in the placebo group, with a maximal prevalence at any time of 4.9 and 1.4 percent, respectively. There was also a higher incidence in the budesonide group of oropharyngeal candidiasis and local irritation of the throat, both well-known side effects of inhaled glucocorticoids. We found no significant effect of budesonide on bone density or the fracture rate, although all subjects were smokers and many of the women were postmenopausal — both of which are well-known risk factors for fracture.

The overall effect of three years of treatment with budesonide on FEV₁ in subjects with mild COPD who continued smoking was quite limited as compared with the beneficial effects of inhaled glucocorticoids in asthma. Although the base-line FEV₁ is significantly related to the prognosis of patients with COPD,²⁰ we cannot extrapolate our findings to assess the potential effect on disability or mortality. The small, overall, one-time beneficial effect on pulmonary function and the possibly more pronounced effect in the subgroup of those who had smoked less must be balanced against the risk of local and systemic side effects.

Funded by a grant from Astra Draco, Lund, Sweden.

APPENDIX

The following physicians enrolled patients in the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease: Belgium — M. DeJonghe, J. Aumann, W. Vincken, and W. DeBacker; Denmark — A. Kok-Jensen, R. Dahl, and P. Tønnesen; Finland — T. Väta, S. Koskinen, P. Tukiainen, P. Saarimäki, and R. Kulmala; Italy — A. Potena, C. Giuntini, A. Foresi, and S. Bianco; the Netherlands — R. van Altena, F.P. Marssen, L. Greefhorst, and P. van Spiegel; Norway — N. Ringdal, C.A. Stendal, G. Vea, V. Sovset, and G.M. Areklest; Spain — R. Rodríguez Roisin, J. Morera Prat, J.M. Marin Trigo, A.A. Farcia-Navarro, and S.A. Leopolodo; Sweden — B. Lundbäck, K. Strom, L. Lazer, and T. Månsson; United Kingdom — J. Gibson, A. Wade, P. Ind, and A. Tattersfield. The following committee members were involved in the study: Safety Committee — J. Boe, Norway; T.B. Conradson, Sweden (Astra Draco); L.M. Fabbri, Italy; and H. Magnussen, Germany. Scientific Committee — A. Tattersfield, United Kingdom; R. Dahl, Denmark; G.J. Huchon, France; B. Mossberg, Sweden; P. Paoletti, Italy; R. Rodríguez Roisin, Spain; and J.C. Yernault, Belgium. The following consultants were involved in the study: P. Quanjer and P. Sterk (spirometry), the Netherlands; J.M. Vonk (statistics), the

Netherlands; and O. Johnell (evaluation of radiographs and dual-energy x-ray absorptiometric measurements), Sweden. The following Astra employees were involved in the study: G. Jönsson (study coordinator), H. Hansson (data entry), M. Brodén (safety evaluation), and M. Hultén (bioanalysis). The national medical monitors were C. Wouters, A. Vandenbroucke, M. Vilstrup, C. Olsen, T. Svahn, E.-L. Kuittilä, C.M. Morelli, M. Schiavon, E. Fanning, M. van den Dobbelaert, V. van Driel-Schroijen, S. Holthe, R. Estévez Navarro, E. Pellicer Thoma, A. MacLean, F. Gien, and E. Story.

REFERENCES

1. Anthonisen NR, Connolly JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: the Lung Health Study. *JAMA* 1994;272:1497-305.
2. Silagy C, Mant D, Fowler G, Lodge M. Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. *Lancet* 1994;343:139-42.
3. Sackis M, Finkelstein R, Cosio MG. Morphological and cellular basis for airflow limitations in smokers. *Eur Respir J* 1994;7:1505-15.
4. Jeffery PK. Structural and inflammatory changes in COPD: a comparison with asthma. *Thorax* 1998;53:129-36.
5. Global Initiative for Asthma. Global strategy for asthma management and prevention. Washington, D.C.: National Heart, Lung, and Blood Institute, 1995. (NIH publication no. 95-3659.)
6. Liewellyn-Jones CG, Harris AJ, Stockley RA. Effect of dexamethasone propionate on sputum of patients with chronic bronchitis and emphysema. *Am J Respir Crit Care Med* 1996;153:616-21.
7. Keatings VM, Jatakanon A, Wordell YM, Barnes PJ. Effects of inhaled and oral glucocorticoids on inflammatory indices in asthma and COPD. *Am J Respir Crit Care Med* 1997;155:542-8.
8. Thompson AB, Mueller MB, Heires AJ, et al. Aerosolized beclomethasone in chronic bronchitis: improved pulmonary function and diminished airway inflammation. *Am Rev Respir Dis* 1992;146:389-95.
9. Confalonieri M, Mainardi E, Della Porta R, et al. Inhaled corticosteroids reduce neutrophilic bronchial inflammation in patients with chronic obstructive pulmonary disease. *Thorax* 1998;53:583-5.
10. Pauwels RA, Lofdahl CG, Pride NB, Postma DS, Laitinen LA, Ohlsson SV. European Respiratory Society study on chronic obstructive pulmonary disease (EUROSCOP): hypothesis and design. *Eur Respir J* 1992;5:1154-61.
11. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernool JC. Lung volumes and forced ventilatory flows: report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal: official statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:5-40.
12. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152:1107-36.
13. Liberman CA, Weiss SR, Bröll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med* 1995;333:1437-43.
14. Reankema TEJ, Schouten JP, Koeter GH, Postma DS. Effects of long-term treatment with corticosteroids in COPD. *Chest* 1996;109:1156-62.
15. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics* 1982;38:963-74.
16. Davidson M, Gilligan DM. Nonlinear models for repeated measurement data. London: Chapman & Hall, 1995.
17. Pinheiro JC, Bates DM. LME and NLME: mixed effects models: methods and classes for S and Splus (1.2) PC Windows. Madison: University of Wisconsin, 1995.
18. Akaike H. Statistical predictor identification. *Ann Inst Stat Math* 1970;203:17.
19. Burrows B. Predictors of loss of lung function and mortality in obstructive lung diseases. *Eur Respir Rev* 1991;1:340-5.
20. Pride NB, Burrows B. Development of impaired lung function: natural history and risk factors. In: Calverley PMA, Pride NB, eds. Chronic obstructive pulmonary disease. London: Chapman & Hall Medical, 1995:69-91.
21. Weir DC, Burge PS. Effects of high dose inhaled beclomethasone dipropionate, 750 micrograms and 1500 micrograms twice daily, and 40 mg per day oral prednisolone on lung function, symptoms, and bronchial hyperresponsiveness in patients with non-asthmatic chronic airflow obstruction. *Thorax* 1993;48:309-16.
22. Kerstjens HAM, Brand PLP, Hughes MD, et al. A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. *N Engl J Med* 1992;327:1413-9.
23. Dompeling E, van Schayck CP, Molema J, Folgering H, van Grunsven PM, van Weel C. Inhaled beclomethasone improves the course of asthma and COPD. *Eur Respir J* 1992;5:945-51.
24. Aulic B, Postma DS, de Montigny JG, van der Mark TW, Boersma M, Koeter GH. Effects of inhaled budesonide on spirometric values, reversibility, airway responsiveness, and cough threshold in smokers with chronic obstructive lung disease. *Thorax* 1991;46:372-7.
25. Callahan CM, Dittus RS, Katz BP. Oral corticosteroid therapy for patients with stable chronic obstructive pulmonary disease: a meta-analysis. *Ann Intern Med* 1991;114:216-23.
26. Watson A, Lim TK, Joyce H, Pride NB. Failure of inhaled corticosteroids to modify bronchoconstrictor or bronchodilator responsiveness in middle-aged smokers with mild airflow obstruction. *Chest* 1992;101:350-5.
27. Engel T, Heining JM, Madsen O, Hansen M, Weeke ER. A trial of inhaled budesonide on airway responsiveness in smokers with chronic bronchitis. *Eur Respir J* 1989;2:935-9.
28. Eklund O, Hoffman J, Trueb D, Frederick D, McCormick JR. Corticosteroids in COPD: a clinical trial and reassessment of the literature. *Chest* 1986;89:484-90.
29. Paggiaro PL, Dahle R, Bakran I, Frih L, Hollingworth K, Eftimov J. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. *Lancet* 1998;351:773-80. [Erratum, *Lancet* 1998;351:1968.]
30. Postma DS, Sreenivas EJ, van der Weide LT, Shuter HJ. Severe chronic airflow obstruction: can corticosteroids slow down progression? *Eur J Respir Dis* 1985;67:56-64.
31. Postma DS, Peters J, Sreenivas EJ, Shuter HJ. Moderately severe chronic airflow obstruction: can corticosteroids slow down progression? *Eur Respir J* 1988;1:22-6.
32. Dompeling E, van Schayck CP, van Grunsven PM, et al. Slowing the deterioration of asthma and chronic obstructive pulmonary disease observed during bronchodilator therapy by adding inhaled corticosteroids: a 4-year prospective study. *Ann Intern Med* 1993;118:770-8.
33. Capewell S, Reynolds S, Shuttleworth D, Edwards C, Finlay AY. Purpura and dermal thinning associated with high dose inhaled corticosteroids. *BMJ* 1990;300:1548-51.
34. Mak VHP, Melcher R, Spiro SG. Easy bruising as a side-effect of inhaled corticosteroids. *Eur Respir J* 1992;5:1068-74.

EFFECT OF SYSTEMIC GLUCOCORTICOIDS ON EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

DENNIS E. NIEWOEHNER, M.D., MARCIA L. ERBLAND, M.D., ROBERT H. DEUPREE, Ph.D., DOROTHEA COLLINS, Sc.D.,
NICHOLAS J. GROSS, M.D., Ph.D., RICHARD W. LIGHT, M.D., PAULA ANDERSON, M.D.,
AND NANCY A. MORGAN, R.Ph., M.B.A.

FOR THE DEPARTMENT OF VETERANS AFFAIRS COOPERATIVE STUDY GROUP*

ABSTRACT

Background and Methods Although their clinical efficacy is unclear and they may cause serious adverse effects, systemic glucocorticoids are a standard treatment for patients hospitalized with exacerbations of chronic obstructive pulmonary disease (COPD). We conducted a double-blind, randomized trial of systemic glucocorticoids (given for two or eight weeks) or placebo, in addition to other therapies, for exacerbations of COPD. Most other care was standardized over the six-month period of follow-up. The primary end point was treatment failure, defined as death from any cause or the need for intubation and mechanical ventilation, readmission to the hospital for COPD, or intensification of drug therapy.

Results Of 1840 potential study participants at 25 Veterans Affairs medical centers, 271 were eligible for participation and were enrolled; 80 received an eight-week course of glucocorticoid therapy, 80 received a two-week course, and 111 received placebo. About half the potential participants were ineligible because they had received systemic glucocorticoids in the previous 30 days. Rates of treatment failure were significantly higher in the placebo group than in the two glucocorticoid groups combined at 30 days (33 percent vs. 23 percent, $P=0.04$) and at 90 days (48 percent vs. 37 percent, $P=0.04$). Systemic glucocorticoids (in both groups combined) were associated with a shorter initial hospital stay (8.5 days, vs. 9.7 days for placebo; $P=0.03$) and with a forced expiratory volume in one second that was about 0.10 liter higher than that in the placebo group by the first day after enrollment. Significant treatment benefits were no longer evident at six months. The eight-week regimen of therapy was not superior to the two-week regimen. The patients who received glucocorticoid therapy were more likely to have hyperglycemia requiring therapy than those who received placebo (15 percent vs. 4 percent, $P=0.002$).

Conclusions Treatment with systemic glucocorticoids results in moderate improvement in clinical outcomes among patients hospitalized for exacerbations of COPD. The maximal benefit is obtained during the first two weeks of therapy. Hyperglycemia of sufficient severity to warrant treatment is the most frequent complication. (N Engl J Med 1999;340:1941-7.)
©1999, Massachusetts Medical Society.

PATIENTS with chronic obstructive pulmonary disease (COPD) frequently have exacerbations that require hospitalization. Hospital treatment for this common condition is associated with high costs and relatively poor outcomes.¹ In addition to antibiotics, oxygen, and bronchodilators, most hospitalized patients receive systemic glucocorticoids. Less severely ill patients often receive oral glucocorticoids as outpatients.

Systemic glucocorticoids improve outcomes in patients with acute asthma,² but their clinical efficacy in the treatment of COPD is less clear. Two small trials suggested that several days of therapy with systemic glucocorticoids improved the forced expiratory volume in one second (FEV₁) during exacerbations of COPD.^{3,4} Another trial found that a single dose of methylprednisolone did not improve spirometric results over the succeeding five hours.⁵ None of these trials were explicitly designed to evaluate clinical outcomes. The role of systemic glucocorticoids in patients with stable COPD is similarly unclear.⁶

Adverse effects of the short-term administration of systemic glucocorticoids include secondary infections, hyperglycemia, and a range of mood and behavioral changes.⁷ Long-term therapy may cause osteoporosis, cataracts, hypertension, myopathy, and adrenal insufficiency.

We conducted a randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy of systemic glucocorticoids for exacerbations of COPD. The principal objective was to determine rates of treatment failure. A secondary goal was to determine the optimal duration of treatment.

METHODS

The Human Rights Committee of the Veterans Affairs Cooperative Studies Program and the institutional review boards of the participating medical centers approved this study. All patients gave written informed consent.

From the Veterans Affairs medical centers in Minneapolis (D.E.N.), Little Rock, Ark. (M.L.E., P.A.), Hines Ill. (N.J.G.), and Long Beach, Calif. (R.W.L.); the Cooperative Studies Program Coordinating Center, West Haven, Conn. (R.H.D., D.C.); and the Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, N.M. (N.A.M.). Address reprint requests to Dr. Niewoehner at the Pulmonary Section (111N), Veterans Affairs Medical Center, 1 Veterans Dr., Minneapolis, MN 55417, or at niewo001@maroon.tc.umn.edu.

*Other investigators who participated in the study are listed in the Appendix.

Study Design

We designed this study to assess the equivalence of two approaches to the treatment of COPD.¹² Systemic glucocorticoids are the standard therapy for hospitalized patients with COPD, even though they have adverse effects. Therefore, the withholding of glucocorticoids may be viewed as an experimental intervention associated with no glucocorticoid-related complications. The planning committee settled on a 7.5 percent absolute difference in the rate of treatment failure as the clinically meaningful upper limit. In other words, withholding glucocorticoids would be considered the preferred treatment if the results showed a difference in the failure rate (the rate with placebo minus the rate with active treatment) of 7.5 percent or less. The secondary objective was to assess the equivalence of two different periods of therapy (two and eight weeks). The follow-up period lasted for six months from the time of enrollment. A detailed description of the rationale for the study, its design, the protocol, and the planned analyses is provided elsewhere.¹³

Study Population

All patients admitted to participating Veterans Affairs medical centers for exacerbations of COPD were potential subjects. The principal inclusion criteria were a clinical diagnosis of exacerbation of COPD, an age of 50 years or more, a history of 30 pack-years or more of cigarette smoking, and either an FEV₁ of 1.50 liters or less or an inability to undergo spirometry because of dyspnea. The principal exclusion criteria were a diagnosis of asthma, use of systemic glucocorticoids within the preceding 30 days, coexisting medical conditions that made survival for at least 1 year unlikely, and inability to give informed consent. We obtained base-line data on respiratory disease and other pertinent aspects of the medical history by means of a questionnaire.¹⁴

Treatments

We randomly assigned patients within 12 hours after presentation to one of three treatment groups. The first group received eight weeks of glucocorticoid therapy, consisting of intravenous methylprednisolone (Solu-Medrol, Pharmacia & Upjohn, Kalamazoo, Mich.) (given in a dose of 125 mg every 6 hours for 72 hours) followed by once-daily oral prednisone (60 mg on study days 4 through 7, 40 mg on days 8 through 11, 20 mg on days 12 through 43, 10 mg on days 44 through 50, and 5 mg on days 51 through 57). The second group received two weeks of glucocorticoid therapy, consisting of intravenous methylprednisolone (125 mg every 6 hours for 72 hours), followed by oral prednisone (60 mg on days 4 through 7, 40 mg on days 8 through 11, and 20 mg on days 12 through 15), with placebo capsules on study days 16 through 57. The third group received placebo, consisting of an equivalent volume of intravenous 5 percent dextrose solution (every 6 hours for 72 hours), followed by placebo capsules on days 4 through 57. Randomization was stratified according to hospital with a permuted-block scheme; 40 percent of the patients were assigned to the placebo group, 30 percent to the eight-week glucocorticoid group, and 30 percent to the two-week glucocorticoid group.

The Veterans Affairs Cooperative Studies Clinical Research Pharmacy Coordinating Center distributed the study medications. Designated research pharmacists dispensed the intravenous medications in a blinded fashion. All patients received the same number of identical-appearing study capsules in blister packs. We assessed compliance on the basis of capsule counts.

The patients remained hospitalized for at least three days for intravenous therapy, after which they received capsules of prednisone or placebo for eight weeks. Hospital staff decided the date of discharge after three days of intravenous therapy. All the patients received a broad-spectrum antibiotic for seven days. For the entire six-month period, the patients were required to use an inhaled β -adrenergic agonist (two puffs from a metered-dose inhaler or a nebulizer treatment at least four times daily), inhaled ipratro-

pium bromide (two puffs from a metered-dose inhaler or a nebulizer treatment at least four times daily), and starting on day 4, inhaled triamcinolone acetonide (eight puffs daily in divided doses; or its equivalent). Use of theophylline, high-dose inhaled glucocorticoids (more than eight puffs daily of triamcinolone acetonide or its equivalent), and open-label systemic glucocorticoids was not allowed. Treatment was considered to have failed if any of the forbidden medications were prescribed. Other medications were permitted according to medical need. We evaluated the patients on each of the first three hospital days and at two weeks, eight weeks, and six months. We continued to obtain follow-up data for patients in whom the study drug had been withdrawn because of treatment failure or for other reasons. If a patient missed a visit, we collected data by mail, telephone, or a review of medical records.

End Points

The primary end point, a first treatment failure, was defined as death from any cause or the need for intubation and mechanical ventilation, readmission because of COPD, or intensification of pharmacologic therapy. The patients' primary physicians made all the clinical decisions. We defined intensification of pharmacologic therapy as the prescription of open-label systemic glucocorticoids, high-dose inhaled glucocorticoids (more than eight puffs per day of triamcinolone acetonide or its equivalent), theophylline, or any combination of these three therapies. When multiple failures occurred on the same day, the assignment to the category of first failure was hierarchical, in the following descending order: death, intubation, readmission, and intensification of therapy. When a primary end point (other than death) was reached, the study treatment was terminated, and usual medical care was resumed.

Secondary end points were a change in FEV₁, the length of the hospital stay, and death from any cause during the six months of follow-up. The patients underwent spirometry at base line; on days 1, 2, and 3; and at the two-week, eight-week, and six-month visits. All centers performed spirometry (model 922, SensorMedics, Yorba Linda, Calif.) according to standard recommendations.¹⁵ We calculated the initial hospital stay as the period from the day of admission to the day of discharge or transfer to an extended-care facility.

Complications

We evaluated the patients for any possible adverse effects of treatment at each visit. As described elsewhere,¹⁶ the diagnosis of hyperglycemia, hypertension, secondary infection, upper gastrointestinal bleeding, or acute psychiatric illness required a consultation, an invasive procedure, or initiation of a specific therapy. We also questioned the patients about other possible adverse events.

Statistical Analysis

The base-line characteristics of the patients in the three treatment groups were compared by means of analysis of variance for continuous variables and the chi-square test for categorical variables.¹⁷ All comparisons of results were based on the intention-to-treat principle. Treatment comparisons were made with the use of a two-step procedure: if the findings for the two-week and the eight-week groups were found to be equivalent, these two groups were combined into a single active-treatment group for comparison with placebo. Comparisons were made at 30, 90, and 182 days after the start of treatment. Treatment failure, the primary end point, was analyzed with use of the upper limit of a one-sided 95 percent confidence interval to determine therapeutic equivalence¹⁸ and a two-sided log-rank test to compare differences between curves for the cumulative failure rate.¹⁹ Values for FEV₁ in the glucocorticoid and placebo groups were compared by analysis of variance, and hospital stays were compared with use of the Wilcoxon two-sample rank test.²⁰ A complication rate was defined as the proportion of patients who had one or more episodes of a complication during the six months of follow-up. Logistic-regression analysis was used

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 271 PATIENTS ACCORDING TO TREATMENT ASSIGNMENT.*

CHARACTERISTIC	PLACEBO (N=111)	GLUCOCORTICOID FOR 2 WK (N=80)	GLUCOCORTICOID FOR 8 WK (N=80)
Age — yr	67.8±10.0	67.1±10.6	68.1±6.8
Male sex — no.	111	80	77
White race — no.	99	59	68
Cough — no. (%)	65 (59)	41 (51)	43 (54)
Sputum production — no. (%)	74 (67)	54 (68)	52 (65)
Wheezing — no. (%)	98 (88)	70 (88)	72 (90)
No. of chest colds per year — no. (%)			
None	17 (15)	17 (21)	14 (18)
1 or 2	64 (58)	51 (64)	50 (62)
≥3	30 (27)	12 (15)	16 (20)
Smoked in past 3 mo — no. (%)	56 (50)	42 (52)	40 (50)
Total cigarette smoking — pack-yr	77.0±35.5	67.3±31	80.9±43.8†
Regular medications — no. (%)			
Inhaled beta-adrenergic agonist	96 (86)	66 (83)	72 (90)
Inhaled anticholinergic drug	81 (73)	47 (59)	58 (73)
Oral beta-adrenergic agonist	12 (11)	4 (5)	7 (9)
Theophylline	37 (33)	26 (32)	30 (38)
Inhaled glucocorticoids	49 (44)	39 (49)	40 (50)
Use of oxygen at home — no. (%)	20 (18)	12 (15)	15 (19)
Hospitalization for COPD in previous 2 yr — no. (%)	73 (66)	51 (64)	60 (75)
Prior use of systemic glucocorticoids — no. (%)	52 (47)	30 (38)	46 (58)‡
Other illnesses — no. (%)			
Diabetes mellitus	5 (5)	12 (15)	11 (14)‡
History of ulcer	23 (21)	19 (24)	16 (20)
Hypertension	44 (40)	39 (49)	39 (49)
Disabling heart disease	13 (12)	8 (10)	8 (10)
Disabling arthritis	12 (11)	10 (12)	15 (19)
History of psychiatric disorder requiring hospitalization	13 (12)	9 (11)	9 (11)
FEV ₁ — ml‡	750±271	772±286	785±288
Time from presentation to randomization — hr	3.7±2.6	3.8±2.6	3.7±2.2

*Plus-minus values are means ±SD.

†P<0.05 for differences among groups by analysis of variance for continuous variables and by the chi-square test for categorical variables.

‡Data were available for 101 patients in the placebo group, 73 in the two-week glucocorticoid group, and 72 in the eight-week glucocorticoid group.

to identify variables that predicted treatment failure within six months.¹⁹ All reported P values are two-tailed.

RESULTS

Enrollment began in November 1994 and concluded in October 1996, one year ahead of schedule. On the basis of interim analyses, the Veterans Affairs Cooperative Studies Evaluation Committee recommended termination of enrollment at that time.

Study Population

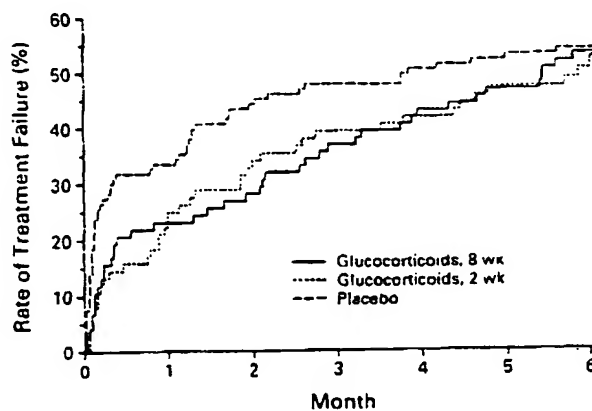
A total of 1840 potential patients at 25 Veterans Affairs medical centers were screened for the study, of whom 271 were found to be eligible and were enrolled. The enrollment rate was lower than had been projected,¹⁰ largely because of a substantial decline in admissions for COPD throughout the Veterans Affairs medical system and an unexpectedly high rate of exclusion because of recent use of systemic glucocorticoids. Among the patients who were screened, 49.9

percent had taken systemic glucocorticoids in the previous 30 days. Other common reasons for exclusion included unwillingness or inability to participate (23.2 percent), a history of less than 30 pack-years of smoking (14.6 percent), and coexisting medical conditions expected to limit survival (18.4 percent).

Eighty patients were assigned to receive glucocorticoid therapy for eight weeks, 80 were assigned to receive glucocorticoid therapy for two weeks, and 111 were assigned to receive placebo. The three treatment groups were similar with respect to base-line characteristics (Table 1). There were small differences in total pack-years of cigarette smoking, prior use of systemic glucocorticoids, and the prevalence of diabetes mellitus.

Discontinuation of Study Drugs and Compliance

Study drugs were discontinued for reasons other than a primary end point in 10 patients assigned to placebo (9 percent), 10 assigned to two weeks of



No. at Risk				
Glucocorticoids, 8 wk	80	61	50	21
Glucocorticoids, 2 wk	80	59	46	20
Placebo	111	74	58	39

Figure 1. Kaplan-Meier Estimates of the Rate of First Treatment Failure at Six Months, According to Treatment Group.

glucocorticoids (12 percent), and 5 assigned to eight weeks of glucocorticoids (6 percent). Follow-up data were complete for 19 of these 25 patients. All available data were included in the analyses. On the basis of counts of returned study capsules, the compliance rate was 89 percent in the placebo group, 85 percent in the two-week glucocorticoid group, and 87 percent in the eight-week glucocorticoid group.

Primary Outcomes

Figure 1 shows Kaplan-Meier estimates of rates of first treatment failure for the three study groups, and Table 2 shows the reasons for treatment failure at 30, 90, and 182 days. At least one treatment failure occurred in approximately half the patients. Intensification of therapy was the most common reason for treatment failure, accounting for 70 percent of the total failures at 30 days, 62 percent at 90 days, and 58 percent at 182 days. When therapy was intensified, physicians administered open-label systemic glucocorticoids in more than 75 percent of cases.

The trial did not demonstrate equivalence of outcomes at any time. When the upper limits of one-sided confidence intervals are used to compare failure rates between groups, the results show that the withholding of glucocorticoids may have increased treatment-failure rates by as much as 20 percent at 30 days, 21 percent at 90 days, and 12 percent at 182 days. All values exceeded the limit of 7.5 percent set by the protocol.

As compared with placebo, glucocorticoids significantly reduced the rate of first treatment failure at 30 days (23 percent vs. 33 percent, $P=0.04$) and 90 days (37 percent vs. 48 percent, $P=0.04$) (Table 2). Treatment-failure rates did not differ significantly at six months (51 percent in the combined glucocorticoid groups vs. 54 percent in the placebo group, $P=0.58$). The duration of glucocorticoid therapy (two weeks or eight weeks) had no significant effect on the rate of treatment failure at any time.

Length of Hospitalization

The average length of the initial hospitalization was significantly longer in the placebo group than in the combined glucocorticoid groups (9.7 vs. 8.5 days, $P=0.03$). After the initial hospitalization, patients in the placebo group spent an average of 2.0 days in the hospital because of COPD, as compared with 1.9 days for patients in the glucocorticoid groups ($P=0.98$). Glucocorticoid-treated patients, on average, spent more time in the hospital for reasons other than COPD than did patients receiving placebo (4.4 vs. 1.2 days, $P=0.07$).

Spirometric Findings

FEV₁ improved significantly faster in the patients who received systemic glucocorticoids than in those who received placebo (Fig. 2). The maximal difference, approximately 0.10 liter, was evident by the first day after enrollment. By the end of two weeks, FEV₁ did not differ significantly between the active-treatment and placebo groups.

TABLE 2. CUMULATIVE PRIMARY OUTCOMES ACCORDING TO TREATMENT ASSIGNMENT.

OUTCOME	PLACEBO (N=111)	GLUCO- CORTICOID FOR 2 WK	GLUCO- CORTICOID FOR 8 WK	P VALUE*
		(N=80)	(N=80)	
		number (percent)		
30 days				
Death	3 (3)	0	2 (2)	
Intubation	3 (3)	2 (2)	1 (1)	
Readmission for COPD	5 (5)	4 (5)	2 (2)	
Intensification of therapy	26 (23)	13 (16)	13 (16)	
Total	37 (33)	19 (24)	18 (22)	0.04
90 days				
Death	4 (4)	2 (2)	2 (2)	
Intubation	3 (3)	3 (4)	1 (1)	
Readmission for COPD	13 (12)	8 (10)	6 (8)	
Intensification of therapy	33 (30)	17 (21)	20 (25)	
Total	53 (48)	30 (38)	29 (36)	0.04
182 days				
Death†	4 (4)	2 (2)	3 (4)	
Intubation	3 (3)	3 (4)	2 (2)	
Readmission for COPD	17 (15)	12 (15)	13 (16)	
Intensification of therapy	36 (32)	22 (28)	24 (30)	
Total	60 (54)	39 (49)	42 (52)	0.58

*P values are for comparisons of the placebo group with the combined glucocorticoid groups, by the log-rank test.

†Only deaths that were counted as primary outcomes are listed. The total numbers of deaths during six months of follow-up were 11 in the placebo group and 13 in the glucocorticoid groups.

Death from All Causes

Over the six months of follow-up, 11 of the 111 patients receiving placebo and 13 of the 160 receiving glucocorticoids died ($P=0.61$). Seven deaths in the placebo group and six in the combined glucocorticoid groups were attributed to COPD.

Complications

Table 3 shows the reported complications for each treatment group over the six months. A greater proportion of patients in the glucocorticoid groups than in the placebo group had hyperglycemia requiring treatment (15 percent vs. 4 percent, $P=0.002$). Twenty-two of the 24 episodes in the glucocorticoid groups occurred during the first 30 days of follow-up. Sixteen of the 24 glucocorticoid-treated patients with hyperglycemia were known to have diabetes. The patients who received glucocorticoids also had more adverse events classified as "other" ($P=0.04$); these included 41 separate symptoms or conditions, most of which were not thought to be caused by glucocorticoids. Reported rates of secondary infection did not differ significantly among the three groups, but the eight-week glucocorticoid group had the highest proportion of patients with serious infections. Eleven of the patients in this group were rehospitalized with a primary diagnosis of infection; 9 of the 11 had pneumonia. Only four patients in the placebo

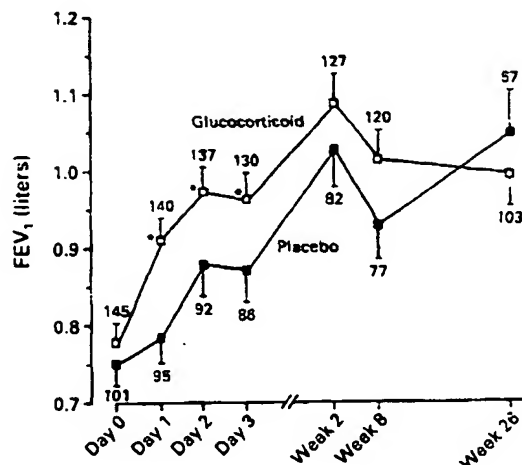


Figure 2. Mean Forced Expiratory Volume in One Second (FEV₁) at Selected Times According to Treatment Group.

The two-week and eight-week glucocorticoid groups have been combined. The numbers at each time point are the numbers of patients in each group for whom data were available. The asterisks denote $P<0.05$ for the comparison with placebo. The bars indicate standard errors.

TABLE 3. COMPLICATIONS OF TREATMENT DURING THE SIX-MONTH FOLLOW-UP PERIOD.

COMPLICATION	PLACEBO (N=111)	GLUCOCORTICOID	GLUCOCORTICOID	P VALUE*
		FOR 2 WK	FOR 8 WK	
		(N=80)	(N=80)	
		number (percent)		
Hyperglycemia	4 (4)	14 (18)	10 (12)	0.002
Gastrointestinal bleeding	5 (5)	0	3 (4)	0.21
Secondary infection	19 (17)	12 (15)	18 (22)	0.73
Hypertension	4 (4)	6 (8)	4 (5)	0.33
Psychiatric disorder	3 (3)	5 (6)	2 (2)	0.47
Other adverse events†	16 (14)	18 (22)	21 (26)	0.04

*P values are for comparisons of the placebo group with the combined glucocorticoid groups, by the chi-square test.

†This category includes 41 different symptoms or conditions.

group and one in the two-week glucocorticoid group were rehospitalized for infection.

Subgroup Analyses

As specified by the protocol, we performed subgroup analyses for the following variables: base-line FEV₁, theophylline use before randomization, hospi-

- investigator), P. Kaul (coprincipal investigator), and R. Varano, Brooklyn, N.Y.; S. Sethi (principal investigator), and P. DiMarzio, Buffalo, N.Y.; R. Keller, Hines, Ill.; M. Reinoso (principal investigator) and P. Guillet, Houston; G. Bhaskar (principal investigator) and H. Hermesman, Lake City, Fla.; G. San Pedro (coprincipal investigator) and L. Frazier, Little Rock, Ark.; J. Despara, Long Beach, Calif.; K. Rice (principal investigator) and F. Leschke, Minneapolis; A. Fulambarker (principal investigator) and D. Ferguson, North Chicago, Ill.; P. Krumpke (principal investigator) and R. Weldon, Reno, Nev.; J. Liu (principal investigator) and T. Thompson, Salem, Va.; M. Habib (principal investigator) and T. Vincent, Tucson, Ariz.; S. Santiago (principal investigator), D. Boyd, and L. Robinson, West Los Angeles, Calif.; J. Sampson (principal investigator), Alexandria, La.; F. Al-Bazzaz (principal investigator), Chicago (West Side); M. Nelson (principal investigator), Kansas City, Mo.; J. McCormick (principal investigator) and S. Sharary, Lexington, Ky.; M. Tenholder (principal investigator), Memphis, Tenn.; W. Davis (principal investigator) and Z. She, Augusta, Ga.; P. Cariba (principal investigator), Miami; B. Gray (principal investigator) and K. Laughlin, Oklahoma City; and C. Arwood (principal investigator), Pittsburgh.
- ### REFERENCES
1. Connors AF Jr, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. *Am J Respir Crit Care Med* 1996;154:959-67. [Erratum, *Am J Respir Crit Care Med* 1997;155:386.]
 2. Rowe BH, Keller JL, Ozman AD. Effectiveness of steroid therapy in acute exacerbations of asthma: a meta-analysis. *Am J Emerg Med* 1992;10:301-10.
 3. Albert RK, Martin TR, Lewis SW. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. *Ann Intern Med* 1980;92:753-8.
 4. Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med* 1996;154:407-12.
 5. Emerson CL, Connors AF, Lukens TW, May ME, Effron D. A randomized controlled trial of methylprednisolone in the emergency treatment of acute exacerbations of COPD. *Chest* 1989;95:563-7.
 6. Callahan CM, Dittus RS, Katz BP. Oral corticosteroid therapy for patients with stable chronic obstructive pulmonary disease: a meta-analysis. *Ann Intern Med* 1991;114:216-23.
 7. McEvoy CE, Niewoehner DE. Adverse effects of corticosteroid therapy for COPD: a critical review. *Chest* 1997;111:732-43.
 8. Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trial to assess equivalence: the importance of rigorous methods. *BMJ* 1996;313:36-9. [Erratum, *BMJ* 1996;313:550.]
 9. Ware JH, Antman EM. Equivalence trials. *N Engl J Med* 1997;337:1159-61.
 10. Erbland ML, Drupree RH, Niewoehner DE. Systemic Corticosteroids in Chronic Obstructive Pulmonary Disease Exacerbations (SCCOPE): rationale and design of an equivalence trial. *Control Clin Trials* 1998;19:404-17.
 11. Epidemiology Standardization Project. II. Recommended respiratory disease questionnaires for use with adults and children in epidemiological research. *Am Rev Respir Dis* 1978;118:Suppl:7-53.
 12. Standardization of spirometry — 1987 update: statement of the American Thoracic Society. *Am Rev Respir Dis* 1987;136:1285-98.
 13. Snedecor GW, Cochran WG. Statistical methods. 8th ed. Ames: Iowa State University Press, 1989.
 14. Durrleman S, Simon R. Planning and monitoring of equivalence studies. *Biometrics* 1990;46:329-36.
 15. Cox DR, Oakes D. Analysis of survival data. London: Chapman & Hall, 1984.
 16. Conn HO, Poyard T. Corticosteroids and peptic ulcer disease: meta-analysis of adverse events during steroid therapy. *J Intern Med* 1994;236:619-32.
 17. Smylie HC, Connolly CK. Incidence of serious complications of corticosteroid therapy in respiratory disease: a retrospective survey of patients in the Brompton Hospital. *Thorax* 1968;23:571-81.
 18. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis* 1989;11:954-63.
 19. Laan RFJM, van Riel PLGM, van de Putte LBA, van Erning LJTO, van't Hof MA, Lemmens JAM. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis: a randomized, controlled study. *Ann Intern Med* 1993;119:963-8.
 20. McEvoy CE, Ensrud KE, Bender E, et al. Association between corticosteroid use and vertebral fractures in older men with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:704-9.
 21. Lederle FA, Pluhar RB, Joseph AM, Niewoehner DE. Tapering of corticosteroid therapy following exacerbation of asthma: a randomized, double-blind, placebo-controlled trial. *Arch Intern Med* 1987;147:2201-3.
 22. O'Driscoll BR, Kaira S, Wilson M, Pickering CAC, Carroll KB, Woodcock AA. Double-blind trial of steroid tapering in acute asthma. *Lancet* 1993;341:324-7.

COMMENTARY

Inhaled steroids in COPD

See page 773

Chronic obstructive pulmonary disease (COPD) is a huge health problem in terms of mortality and morbidity. In the UK, in the 3-year period 1990-92 the numbers of deaths attributable to COPD were 51 500 for men over 65 and 30 000 for women over 65.¹ These numbers far exceed the 1500 to 2000 deaths per year from asthma in the UK. In terms of hospital admissions for adults, COPD is a much greater burden on the health service than is asthma.

Over the past 10 years there has been a substantial change in the management of asthma, with the introduction of management guidelines and their emphasis on the use of inhaled corticosteroids in all patients except those with mild asthma.² These recommendations are firmly backed by data from many clinical trials.

Inhaled steroids improve pulmonary function and symptoms in asthma, enhance quality of life, prevent allergen-induced bronchoconstriction in atopic patients and, when used chronically, increase exercise capacity. An emphasis in recent trials has been on the ability of inhaled corticosteroids to prevent exacerbations or worsening of asthma,³ and it is this effect that accounts for the ability of these agents to prevent hospital admissions and for the increasing circumstantial evidence that inhaled corticosteroids decrease the asthma death rate.^{4,5}

This clinical-trial evidence is supported by research into the effects of inhaled corticosteroids on the pathology of asthma. Airways inflammation in asthma is characterised by an increase in CD4-lymphocyte count, an increase in eosinophil count, a small increase in mast-cell count, thickening of the basement membrane, and disruption of the airway epithelium. Inhaled steroids cause a decrease in the number and state of activation of CD4 cells, eosinophils, and mast cells and restitution of the normal airway epithelium.⁶ There is less evidence that they reverse subepithelial fibrosis.

The evidence that inhaled corticosteroids are of benefit in COPD, either clinically or pathophysiologically, is scanty, yet these agents are widely used in the management of this disorder. This discrepancy is partly due to the inevitable diagnostic confusion between asthma in the elderly and COPD. Another reason is that, faced with a patient for whom few other treatments are of clear-cut benefit, physicians will try a treatment they judge to be safe, even if the likelihood of benefit is low. A third reason is that during acute exacerbations of COPD

systemic steroids may speed recovery, an effect that is taken as evidence that steroids will be of help in that individual in the long term.

In recently published guidelines⁷ on the management of COPD, inhaled corticosteroids are recommended only for those patients who show a clear objective response to a formal trial of either oral or high-dose inhaled steroids. For an unselected group of patients with COPD, a positive trial of steroids is defined as a 15% increase in baseline FEV₁ with an absolute increase of greater than 200 mL. A change of this magnitude is seen in 10-15% of patients with COPD.

COPD is a clinical descriptive term for patients, mostly elderly, who have airflow obstruction that is not relieved completely with therapy. It is caused by at least three distinct pathological processes, which may occur separately or, in many patients, concurrently. These processes are destruction of alveolar walls causing emphysema, chronic bronchitis with hypersecretion of mucus, and chronic asthma.⁸ There are few studies on the airway pathology of COPD, but the pathological features are distinct from those of asthma. In COPD there is a predominance of CD8 cells, an increase in number of neutrophils, no thickening of the basement membrane, and no evidence of disruption of the airway epithelium, but there is an increase in squamous metaplasia.

It is commonly thought that the 15% of patients who respond to steroids represent a group with a substantial chronic asthmatic component. This view is supported by a study⁹ that showed that in patients with a clinical diagnosis of COPD, those with biopsy features of asthma (high number of eosinophils and thickening of the basement membrane) were the ones who improved with high-dose prednisolone over 2 weeks. The limited number of studies of the effect of steroids on airways inflammation in COPD has shown little evidence of an acute anti-inflammatory effect,¹⁰ although there may be some effect on airway protein leakage.¹¹ Taken together the evidence supports the recommendation in the COPD guidelines that patients who show a definite response to steroids (presumed to be those with a component of asthma to their disease) should be treated with inhaled corticosteroids. The unanswered question is how to deal with the remaining 80-90% of patients who do not show a clear-cut response to steroids. This group of patients will not have much improvement in pulmonary function with corticosteroids, so other outcome measures must be used.

Survival in COPD correlates inversely with FEV₁, and

any treatment that slows the accelerated decline in FEV₁ in COPD will be likely to reduce mortality. One question that is the subject of at least two large-scale studies is whether inhaled corticosteroids slow the decline of FEV₁ in patients with COPD. The EUROSCOP study is investigating this issue in mild COPD.¹ Initial results suggest that any effect is small and transitory. The ISOLDE study is investigating the question in a group of patients with more severe COPD.² In shorter-term trials it would be sensible to look at outcome measures such as prevention of exacerbations of COPD (which are a common and important clinical problem), exercise capacity, and quality of life.

The study reported in today's *Lancet* is a comparison of the effects of high-dose inhaled steroids (fluticasone 500 µg twice daily) with placebo over a 6-month treatment period. The primary outcome variable was the exacerbation rate, with secondary outcome variables being symptoms, pulmonary function, 6 min walking distance, and breathlessness. The overall rate of COPD exacerbations was lower than had been predicted from pilot studies, and no significant difference was seen between the groups. However, there seemed to be a shift in severity of exacerbations, with fewer patients in the active-treatment group having severe exacerbations. This possible effect of inhaled steroids in COPD needs to be investigated. There was also a small but clinically and statistically significant improvement in peak expiratory flow rate of 15 L/min in the inhaled-steroid group, and this finding was supported by small improvements in spirometry, symptoms, and walking distance. The individuals recruited had moderately impaired pulmonary function, with less than 8% reversibility in FEV₁ after bronchodilator and no evidence of blood eosinophilia, which might indicate asthma. The only predictor of response that the investigators found was a duration of COPD of greater than 10 years. This earlier onset of symptoms among responders could be interpreted as being due to the contribution of a component of asthma to their airflow obstruction.

The study did not investigate lower doses of inhaled steroids, which may also be effective. There is no indication from the data of a loss of activity over 6 months, but further studies looking at the duration of any effect are needed.

What lessons for clinical practice and research can be drawn from this study? There should be no change in the recommendation in the COPD guidelines that patients who show striking response to oral or inhaled corticosteroid should be treated with inhaled steroids. The study shows that a small absolute improvement in pulmonary function is associated with clinical benefit in terms of symptoms, exercise capacity, and possible severity of exacerbations. If that is so, a reasonable approach would be to lower the threshold for concluding that a patient's illness has undergone a clinically important improvement with inhaled steroids. If after several months of treatment with high-dose inhaled steroids, peak flow improves by 15 L/min or more and the severity and the number of exacerbations fall, the patient should continue on inhaled steroids. If these variables do not improve, there is no compelling reason to continue with inhaled steroids. Since it is difficult to demonstrate clinical predictors of response, an area that may justify further investigation is whether pathological appearances—especially eosinophils or thickened

basement membrane—should be used to predict a response.

The broader implication of this study is that the current treatment of COPD remains extremely unsatisfactory. Obviously, avoidance or cessation of smoking is the key to improving the outlook for patients with COPD. However, even if patients succeed in giving up smoking, there will still be many symptomatic patients for the foreseeable future. It is vital that understanding of the basic mechanisms in COPD improves. Present evidence suggests that inflammation present in COPD is poorly responsive to steroids or that, unlike asthma, this airways inflammation is not the primary problem in the disease. New treatments for COPD are urgently required.³

N C Barnes

Department of Respiratory Medicine, London Chest Hospital, London E2 9JX, UK

- 1 Anon. The geography of COPD mortality in the elderly. London: Lung and Asthma Information Agency, Factsheet 96/1.
- 2 The British Guidelines on Asthma Management 1995. Review and position statement. *Thorax* 1997; 52 (suppl 1).
- 3 Kerrebijn KF, Von Essen-Zandvliet EEM, Neijters HJE. Effect of long-term treatment with inhaled corticosteroids and beta-agonists on bronchial responsiveness in asthmatic children. *J Allergy Clin Immunol* 1987; 79: 653-59.
- 4 Ernst P, Spitzer WD, Suisds S, et al. Risk of fatal and near fatal asthma in relation to inhaled corticosteroid use. *JAMA* 1992; 265: 3462-64.
- 5 Campbell MJ, Cogman GR, Holgate ST, Johnston SL. Age specific trends in asthma mortality in England and Wales, 1983-95: results of an observational study. *BMJ* 1997; 314: 1439-41.
- 6 Djukanovic R. Bronchial biopsies. In: Busse WW, Holgate ST, eds. *Asthma and rhinitis*. Oxford: Blackwell, 1995: 118-29.
- 7 British Thoracic Society guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997; 52 (suppl 5).
- 8 Jeffrey PK. Structural and inflammatory changes in COPD: a comparison with asthma. *Thorax* 1997; 53: 129-36.
- 9 Chanez P, Vignola AM, O'Shaughnessy T, et al. Corticosteroid reversibility in COPD is related to features of asthma. *Am J Respir Crit Care Med* 1997; 155: 1529-34.
- 10 Keatings VM, Jarakanon A, Worsdell YM, Barnes PJ. Effects of inhaled and oral glucocorticoids in inflammatory indices in asthma and COPD. *Am J Respir Crit Care Med* 1997; 155: 542-48.
- 11 Llewellyn-Jones CG, Harris TAJ, Stockley RA. The effect of fluticasone propionate on sputum of patients with chronic bronchitis and emphysema. *Am J Respir Crit Care Med* 1996; 153: 616-21.
- 12 Pauwels RA, Lofdahl CG, Pride NB, Postma DS, Laitinen LA, Ohlsson SV. European Respiratory Society study on chronic obstructive pulmonary disease (EUROSCOP): hypothesis and design. *Eur Respir J* 1992; 5: 1254-61.
- 13 Burge PS, Calverley PMA, Daniels JME. The acute effects of oral prednisolone in patients with COPD in the ISOLDE trial: responders and non-responders. *Am J Respir Crit Care Med* 1996; 153 (suppl 4): A126.
- 14 Barnes PJ. New therapies for chronic obstructive pulmonary disease. *Thorax* 1998; 53: 137-47.

Ankylosing spondylitis, HLA B27, and beyond

Publication of the landmark *Lancet* paper showing the strong association between HLA B27 and ankylosing spondylitis 25 years ago¹ stimulated an avalanche of research into HLA/disease associations. The subsequent weaker associations of HLA B27 with anterior uveitis, reactive arthritis, sacroiliitis, late-onset pauciarticular juvenile chronic arthritis in boys, and inflammatory bowel disease with axial joint involvement suggested a common genetic determinant for a group of disorders already linked as seronegative spondyloarthropathies by the clinical observations and family studies of the late Verna Wright,² and others. Because reactive arthritis can

- 17 Barnes NC, Hallett C, Harns TAJ. Clinical experience with fluticasone propionate in asthma: a meta-analysis of efficacy and systemic activity compared with budesonide and beclomethasone propionate at half the microgram dose or less. *Respir Med* 1998; 92: 95-104.
- 18 Liewellyn-Jones CG, Harris TAJ, Stockley RA. The effect of fluticasone propionate on sputum of patients with chronic bronchitis and emphysema. *Am J Respir Crit Care Med* 1996; 153: 615-21.
- 19 Wilson RC, Jones PW. Long-term reproducibility of Borg scale estimates of breathlessness during exercise. *Clin Sci* 1991; 80: 309-12.
- 20 Peace KE, ed. Biopharmaceutical statistics for drug development. New York: Marcel Dekker, 1988: 403-57.
- 21 van Elteren PH. On the combination of independent two sample tests of Wilcoxon. *Bull Int Stat Inst* 1960; 37: 351-61.
- 22 Boyd G, Morice AH, Pounstford JC, Siebert M, Pestis N, Crawford C. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1997; 10: 815-21.
- 23 Callahan C, Dimas RS, Katz BP. Oral corticosteroid therapy for patients with stable chronic obstructive pulmonary disease: a meta-analysis. *Ann Intern Med* 1993; 118: 770-78.
- 24 Rutten-van Molken MPMA, Jansen MCC, van Doorslaer EKA, et al. Costs and effects of inhaled corticosteroids and bronchodilators in asthma and COPD. *Am J Respir Crit Care Med* 1995; 151: 975-82.
- 25 Keatings VM, Jarakanon A, Worsdell YM, Barnes P. Effects of inhaled oral glucocorticoids in inflammatory indices in asthma and COPD. *Am J Respir Crit Care Med* 1997; 155: 542-43.
- 26 Renkema TEJ, Schouten JP, Koeter GH, Postma DS. Effects of long-term treatment with corticosteroids in COPD. *Chest* 1996; 109: 1156-62.
- 27 Weiner P, Weiner M, Azgad Y, Zamir D. Inhaled budesonide therapy for patients with stable COPD. *Chest* 1995; 108: 1566-71.
- 28 Thompson AB, Mueller MB, Heires AJ, et al. Aerosolised beclomethasone in chronic bronchitis: improved pulmonary function and diminished airway inflammation. *Am Rev Respir Dis* 1992; 146: 389-95.
- 29 Chanex P, Vignola AM, O'Shaughnessy T, et al. Corticosteroid therapy in COPD is related to features of asthma. *Am J Respir Crit Care Med* 1997; 155: 1529-34.
- 30 van Schayck CP, van Grunsven PM, Dekhuijzen PNR. Do patients with COPD benefit from treatment with inhaled corticosteroids? *Eur Respir J* 1996; 9: 1969-72.
- 31 Pauwels RA, Lofdahl CG, Pride NB, Postma DS, Laijnen LA, Ohlsson SV. European Respiratory Society study on chronic obstructive pulmonary disease (Euroscop): hypothesis and design. *Eur Respir J* 1992; 5: 1254-61.
- 32 Burge PS, Calverley PMA, Daniels JE. The acute effects of oral prednisolone in patients with COPD in the ISOLDE trial: responders and non-responders? *Am J Respir Crit Care Med* 1996; 153: 126.

Highlights of a symposium on chronic obstructive pulmonary disease held at the National Heart and Lung Institute, London, July 7-8, 1998.

COPD: New Developments and Therapeutic Opportunities

by Peter Norman

A fascinating meeting on chronic obstructive pulmonary disease (COPD) was arranged by Profs. Peter Barnes and Neil Pride, of the National Heart and Lung Institute, London, U.K. (NHLI), to highlight the growing significance of COPD, to emphasize the paucity of our knowledge of the disease mechanisms and to address the problems of treating the disease. To this end, the deficiencies of current therapies and potential novel approaches were discussed.

The disease

Peter Barnes gave the introductory lecture. COPD is a disease characterized by irreversible airways obstruction and encompasses both chronic bronchitis and emphysema. It has a major economic impact, being responsible for 10-15% of sickness benefit in the developed world. It is responsible for 25% of deaths in the United States, and the WHO is currently predicting that it will be the third major cause of death in the world within 20 years.

Summary

The deficiencies of current therapies and the potential benefits of novel approaches to chronic obstructive pulmonary disease (COPD) were reviewed at a symposium organized at the National Heart and Lung Institute, London, U.K., July 7-8, 1999. Several speakers discussed different facets of the disease. The keynote lecture dealt with two major, but distinct themes: the utility of computerized tomographic scanning as both a quantitative and a qualitative tool and the recent observation that retinoic acid could produce new alveolar growth, emanating from ducts, in hamsters when it was administered after instillation of elastase. Regarding current therapeutic approaches, bronchodilators are the mainstay of existing therapy, while the use of mucolytics varies markedly between countries. The role of steroids in the treatment of COPD is confused. There is surprisingly little evidence of any clinical benefit from the use of antibiotics. Potential future therapies include M_2 -selective muscarinic antagonists, chemotactic mediators, protease inhibitors and antiinflammatory agents. © 1998 Prous Science. All rights reserved.

Prof. Barnes was the first of several speakers to show a slide based on the work of Fletcher and Peto illustrating the progressive decline of forced expiratory volume (FEV_1), a measure of lung function, with age, by 25 ml annually in normal subjects. This is substantially accentuated by smoking, albeit in only a proportion of smokers, and this progressive decline in lung function eventually results in death. Smoking cessation results in a slowing, but not a reversal, of this deterioration.

John Britton (Nottingham University, U.K.) considered the disease's epidemiology. Currently it is substantially more prevalent in men than women, but this is attributed to the historically lower prevalence of smoking in women. Changes in smoking patterns suggest such differences will soon disappear. Smoking is the primary risk factor (83%), although both passive smoking and heavy exposure to dust, for example, in coal miners, are additional risk factors. These risk factors result in COPD being a disease of late middle and old age.

occurring only rarely in the under-45 population.

There are pronounced geographical differences in the incidence of COPD. It is most common in Northern and Eastern Europe with progressively lower frequencies in the United States, Mediterranean Europe and Japan. While such differences may be partially explicable due to differences in diagnosis, there are presumed to be genetic factors also involved. Currently the only known contributory factor is α_1 -antiprotease deficiency.

Different facets of the disease were reviewed by Peter Jeffrey, Terry Tötley, Duncan Rogers (all NHLI) and Rob Stockley (Queen Elizabeth Hospital, Birmingham, U.K.), while Trevor Hansel (NHLI) highlighted the problems of designing appropriate clinical trials. These ideally require the identification of relevant surrogate markers and better-defined endpoints than small changes in the rate of decline of FEV₁ for the long (two- to three-year) phase III studies.

Although it can be difficult to distinguish between asthma and COPD on the basis of lung function measurements, there are major differences in the lung pathology. Bronchitis is characterized by damaged cilia, goblet cell hyperplasia and mucus hypersecretion with stenosed small airways but comparatively little epithelial damage. In emphysema, there is substantial inflammation of the peripheral airways accompanied by significant acinar damage. In both conditions there is extensive infiltration by CD8+ lymphocytes, with a ninefold elevation of lung macrophages and a 100-fold increase in neutrophil levels, predominantly within the epithelium.

Associated with this elevation of neutrophils are significant increases in interleukin-8 (IL-8) levels and an increase in proteolytic enzymes, principally neutrophil elastase but also matrix metalloproteinases (MMPs). A key, unanswered, question is which factors are predictive of a predisposi-

tion to COPD. Thus, studies examining cell markers in smokers should only see pronounced changes in a fraction (10–20%) of the patients examined. IL-8 chemotactic activity in sputum from smokers falls into this category, whereas levels of a number of proteolytic enzymes (cathepsin L, collagenase and gelatinase B) are generally elevated in all smokers. There are also some data suggesting that the cytokines IL-1 and tumor necrosis factor- α are involved in the disease pathogenesis.

Excessive mucus secretion is a symptom of the disease, but does not appear to be a causal factor. The presence of excessive mucus allows bacterial colonization, facilitating exacerbations, in addition to obstructing the airways. Once the disease is established, both mucus hypersecretion and mucous cell hyperplasia are observed. While mucolytic agents have the potential to improve mucus clearance, truly effective agents are not available. Two mucin genes, MUC5A and MUC5B, appear to be of major significance in the airways, but their regulation is not yet understood.

The keynote lecture was presented by James Hogg (Vancouver, Canada) and dealt with two major, but distinct themes. He first addressed the utility of computerized tomographic scanning both as a quantitative tool to evaluate the progression of the disease and, more qualitatively, to facilitate identification of nonfunctioning areas of the lung that might be removed in lung volume resection surgery.

Until recently there has been no evidence that therapeutic intervention might be able to reverse, rather than halt, the destruction of lung tissue. The second part of Dr. Hogg's talk addressed the recent observation by Donald and Gloria Massaro that retinoic acid could produce new alveolar growth, emanating from ducts, in hamsters when it was administered after instillation of elastase. Precise measurements are required to observe functional changes in this model.

Dr. Hogg suggested that the changes in the ratio of lung surface to volume mirror those observed early in clinical emphysema. Identifying the critical transcriptional mechanisms involved will undoubtedly become a major research effort, given the significance of the observations by the Massaros. However, he did suggest that it would be desirable to repeat such observations in an animal where alveolar growth stops at birth, such as the guinea pig, which would better model the human condition, where growth stops at four years of age.

Current therapy

An overview of current therapeutic approaches to the treatment of COPD was provided by Philip Ind (NHLI), while Peter Calverley (University Hospital, Liverpool, U.K.) considered alternatives to pharmacological intervention. Neil Pride (NHLI) reviewed the evidence from recent long-term clinical studies with inhaled steroids and Robert Wilson (NHLI) addressed the role of antibiotics in the treatment of exacerbations.

Bronchodilators provide the mainstay of existing therapy, and both inhaled muscarinic antagonists (generally ipratropium bromide) and β_2 -agonists are routinely employed. The effects of members of these two classes are additive, and they are now often administered as a combination preparation. A more recent alternative is the use of q.i.d. ipratropium plus a long-acting β_2 -agonist. While theophylline has beneficial effects, its use in elderly patients is often constrained by side effects.

The use of mucolytics varies markedly between countries. Because of their questionable efficacy, the availability of these drugs is often restricted by regulatory authorities. However, there is some evidence substantiating the efficacy of *N*-acetylcysteine.

The role of steroids in the treatment of COPD is confused. It has been commonly held that they are ineffec-

ive, but they are commonly prescribed by general practitioners. Inhaled formulations are designed for the treatment of asthma, so they do not deliver significant doses of steroids to peripheral lung. Few studies have addressed the role of systemic steroids in treating acute exacerbations, but administration of oral prednisolone for two weeks appears to improve lung function.

Ongoing studies such as EURO-SCOP and ISOLDE have examined the efficacy of three years' treatment with inhaled budesonide. The available results suggest that the benefit is relatively small, but significant improvements in FEV₁ were noted in the first three months of treatment. Fluticasone treatment has also been shown to result in (small) improvements in FEV₁ over a six-month period.

While antibiotics are commonly administered to patients suffering from COPD exacerbations, there is surprisingly little evidence of any clinical benefit from their use. Unless there is bacterial colonization of the lung, by organisms such as *Haemophilus influenzae*, even placebo treatment is effective in over 50% of cases. However, diagnosis of infection requires correct diagnosis from the presence of purulent sputum or, preferably, by culturing bronchial brushings.

There has been a dramatic increase in antibiotic resistance of the common infectious organisms, especially in the United States. There nearly all infections with *Moraxella catarrhalis* are resistant, with 50% of *H. influenzae* resistant and also with high β -lactamase activity, and 24% of *Streptococcus pneumoniae* infections are also resistant. Significant resistance to quinolones has not yet been observed, but it was stressed that indiscriminant use of the new quinolones could lead to substantial problems in treating such cases. New guidelines, currently being agreed, will recommend the use of ciprofloxacin, azithromycin or amoxicillin + clavulanic acid for the

treatment of chronic purulent infections.

The more severe COPD patients are commonly underweight, and it was suggested that this worsens the disease prognosis. Oxygen treatment is beneficial in improving life expectancy in severe patients, but only when they are significantly hypoxemic ($\text{PaO}_2 < 7.3$ kPa). A recently developed radical alternative for emphysema patients is lung volume reduction surgery. If performed carefully, this appears to be at least as effective as a single lung transplant. While a double lung transplant affords improved lung function, it does not improve the disease mortality, in contrast to what occurs in patients with cystic fibrosis.

Potential therapies

Muscarinic antagonists

The identification of distinct muscarinic receptor subtypes and the comprehension of their physiological role has led to the realization that it is less desirable to block the M₂ receptor in treating COPD. Peter Barnes indicated that these act as autoreceptors, and hence blockade of these would tend to counteract the benefits gained by blocking M₂ receptors.

Both Pfizer and Boehringer Ingelheim have developed new selective muscarinic antagonists, but with very different properties. Pfizer has identified both a selective M₁ antagonist, **darifenacin** (Fig. 1), and an M₁/M₂-selective antagonist, **revatropate** (Fig. 1). Both were stated to be short-acting drugs, like ipratropium bromide, and clinical results with revatropate have proved disappointing.

Tiotropium bromide (Boehringer Ingelheim; Fig. 1) has no intrinsic muscarinic receptor selectivity, displaying subnanomolar K_D values at all three receptor subtypes, but has the unusual property of kinetic selectivity with a dissociation half-life of 34.7 hours from M₁ receptors compared to 3.6 hours from M₂ receptors. This drug

behaves as a long-acting and selective antagonist both *in vitro* and in animal studies. In humans, it is well tolerated when administered as a dry powder and produces a dose-related bronchodilatation which lasts for over 24 hours. A four-week phase III study in COPD patients has confirmed the efficacy, and tolerability, of once-daily dosing, with drug effects persisting for a week after cessation of treatment. This drug is rapidly metabolized when swallowed, so side effects are minimal. Peter Barnes stated that oral administration of selective M₁ antagonists produces all the undesirable side effects such as dry mouth. He also indicated that the old muscarinic antagonist **glycopyrronium bromide** (A.H. Robins; Fig. 1) behaves in a similar manner to tiotropium and is now being developed for the treatment of COPD.

Chemotactic mediators

Sputum from COPD patients is highly chemotactic for neutrophils. This is principally due to the presence of high concentrations of the chemokine IL-8 and the eicosanoid leukotriene B₄ (LTB₄), with each accounting for about 40% of the chemotactic activity in sputum. LTB₄ levels are substantially elevated in asymptomatic smokers, and the decline of lung function has been shown to correlate to the neutrophil concentration in sputum.

The effects of LTB₄ could be reduced either via inhibiting its synthesis with lipoxygenase inhibitors or with specific BLT receptor antagonists. Although many lipoxygenase inhibitors have been developed for the treatment of asthma, with Abbott's **zileuton** approved for that indication, there are no reports of their clinical evaluation in COPD. A number of BLT antagonists are currently in clinical development for the treatment of psoriasis (VML-295, Lilly, Vanguard Medica; ONO-4057, Ono) or arthritis (CGS-25019C; Novartis), with no efficacy seen in studies in asthmatics with, for example, LY-293111 (Lilly).

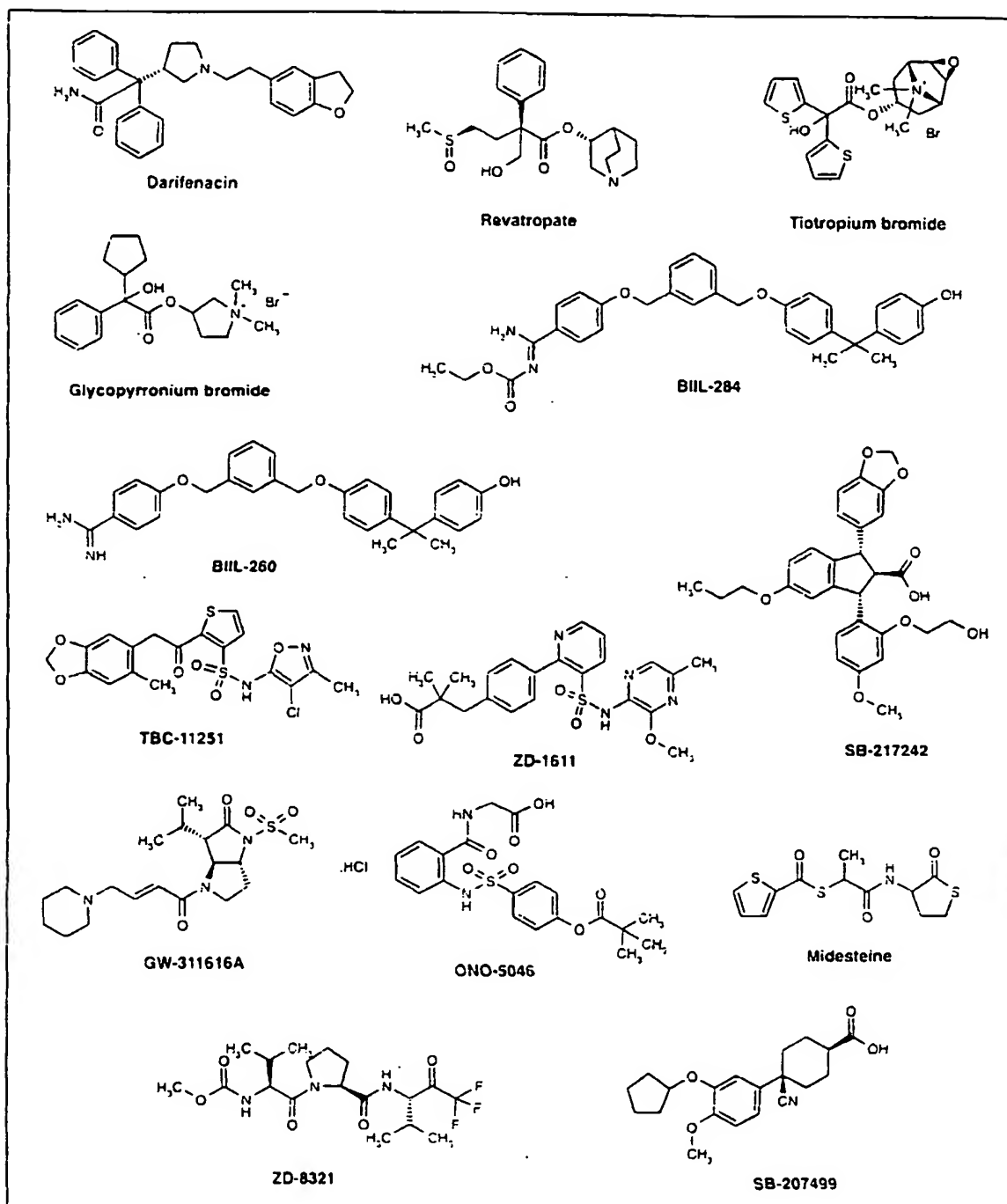


Fig. 1. Structures of compounds discussed at the symposium.

Boehringer Ingelheim has developed a novel antagonist, the phenylguanidine derivative **BIIL-284** (Fig. 1), and has just initiated phase I stud-

ies with the intention of developing this drug for the treatment of COPD. Franz Birke (Ingelheim) described the pharmacological profile of this long-

acting compound. **BIIL-284** is a formate ester prodrug, which is cleaved *in vivo* to the more active free guanidine **BIIL-260** (Fig. 1)

TABLE 1: ACTIVITY OF SELECTED BLT RECEPTOR ANTAGONISTS

DRUG	K _i (nM) (PH)-LTB ₄ BINDING TO HUMAN NEUTROPHILS	ED ₅₀ (mg/kg po) LTB ₄ -INDUCED MOUSE EAR INFLAMMATION	ED ₅₀ (mg/kg po) LTB ₄ -INDUCED NEUTROPENIA IN MONKEYS	t _{1/2} (hours) LTB ₄ -INDUCED NEUTROPENIA IN MONKEYS
BIL-284	150	0.008	0.004	24
BIL-260	1.3	—	—	—
CGS-25019C	0.9	5.5	2.5	1.0
LY-293111 (VML-295)	24	>20	3.1	3.0

Dr. Birke presented data comparing these compounds with two other antagonists (Table 1). In studies in primates, administration of BIL-284 resulted in a greater than 95% inhibition of Mac-1 expression on circulating neutrophils, and a 1-mg/kg oral dose resulted in a greater than 90% inhibition of LTB₄-induced neutropenia 24 hours after dosing. Toxicological studies have failed to show any adverse effects of this drug.

IL-8 is a CXC chemokine acting on both CXCR1 and CXCR2 receptors. These G-protein-coupled receptors, sometimes referred to as IL-8 receptors, are also activated by other chemokines (CXCR1 by GCP-2 and CXCR2 by Gro, NAP-2 and ENA-78), and are heavily expressed on neutrophils but only lightly expressed on eosinophils.

Amanda Proudfoot (Serono, Geneva) reviewed this area and indicated that interferon gamma selectively up-regulates CCR receptors, but not CXCR receptors, on human neutrophils. She and her colleagues have found that chemokines are selectively recognized by glycosaminoglycans. These selectively recognize IL-8 in the following order: heparin > heparan sulfate > chondroitin sulfate; such interactions were suggested to provide a mechanism for localized *in vivo* control of chemokine effects.

Both CXC and CC chemokine antagonists are known that have been produced by modification of the N-terminus. The CCR antagonist MET-RANTES has been used to demonstrate an involvement of CC chemokines in models of asthma and

arthritis. No data on IL-8 antagonists, either peptide analogues or small-molecule nonpeptides, were presented.

There is also a significant body of evidence that implicates the peptide endothelin-1 as playing a pathological role in COPD and especially in pulmonary hypertension. Tony Rebuck (SmithKline Beecham, U.S.A.) reviewed the therapeutic potential of endothelin (ET) antagonists. There is currently no evidence to indicate an elevation in ET levels in the lungs of COPD patients, whereas levels are elevated in patients with chronic hypoxia.

Endothelin antagonists are effective in animal models of hypoxia. The nonselective antagonist SB-217242 (SmithKline Beecham; Fig. 1), at 3.6 mg/day, prevented hypoxia-induced increases in pulmonary artery pressure in a rat model of chronic hypoxia. This compound, like TBC-11251 (Texas Biotechnology; Fig. 1) and ZD-1611 (Zeneca; Fig. 1), is currently in phase II studies for the treatment of pulmonary hypertension, but is also under clinical evaluation for the treatment of COPD. Such studies should help clarify the role of endothelin in lung diseases provided appropriate clinical endpoints are defined.

Protease inhibitors

Activated neutrophils also release high levels of the serine protease elastase. When the normal physiological control mechanisms are defective, this enzyme causes substantial degradation of the extracellular matrix, leading to extensive alveolar damage and eventually resulting in emphysema. Therapeutic approaches to elastase

inhibition were discussed by Robin Smith (Glaxo Wellcome, Stevenage, U.K.). He described the activities of three inhibitors but did not reveal their structures.

Both polypeptide and small-molecule inhibitors have been sought, with much of this effort directed toward the latter. Although both purified and recombinant forms of the natural inhibitor (α_1 -antitrypsin) are available, effective inhibition requires gram quantities in the lung, thus limiting its utility on cost grounds. Aerosol formulations of the smaller peptide SLPI (secretory leukocyte protease inhibitor) are under development by both Synergen and Teijin in full-length and C-truncated forms, respectively, but clinical results were not discussed.

Because elastase is stored in an active form in azurophilic granules within the neutrophil, at a concentration of 5 mM, synthetic inhibitors have been targeted at both extracellular and intracellular elastase. GW-311616A (Glaxo Wellcome; Fig. 1) is a low-molecular-weight inhibitor of intracellular elastase. This compound, in pre-clinical development, is based on a novel template and is orally active in dogs at doses of 0.2–2 mg/kg. It was implied to be more potent *in vivo* than DMP-777 and said to be a slowly reversible inhibitor.

ONO-5046 (Ono), midesteine (Medea Research) and ZD-8321 (Zeneca) (Fig. 1) are all extracellular inhibitors currently reported to be in phase II or III studies for the treatment of emphysema. Midesteine is a weak enzyme inhibitor ($K_i = 1.4 \mu\text{M}$) that is well tolerated in humans but displayed limited efficacy in a four-week study in COPD patients. Glaxo had earlier been investigating compounds with such activity, and both GR-243216 and GR-243214 were described as active, at 3 μg intratracheally, in hamster models of emphysema. GR-243216 was the more potent compound, with a K_i value of 6 nM and a 16-hour duration of action.

David Lomas (Cambridge University, U.K.) described studies on the mechanistic defects in Z α_1 -antitrypsin. This point mutation results in the breaking of an intramolecular salt bridge, and allows the mutant α_1 -antitrypsin to polymerize, in a temperature-dependent manner, rather than inactivate elastase. The resulting protease-antiprotease imbalance results in the genetic form of emphysema. His group's progress in defining the mechanisms involved and delineating the structure of the active site offers new possibilities for rational drug design to prevent the problems that arise from this relatively common genetic disease, which accounts for 1-2% of all cases of emphysema.

Recent studies have shown the lungs of emphysema patients to contain elevated levels of the MMP enzymes gelatinase B and collagenase. These are secreted both from airway epithelium and alveolar macrophages. It remains unclear whether they play a causal role in the disease pathogenesis. Their elevation may result from inactivation of tissue inhibitors of metalloproteases (TIMP). It has been suggested that collagenase activity in lavage fluid may be a better marker for the diagnosis of emphysema than elastase activity. Such observations suggest that MMP inhibitors may have a role to play in the treatment of COPD.

Antiinflammatory agents

Three possible approaches to the reduction of inflammation were discussed. The use of novel antioxidants to attenuate the damage caused by cigarette smoke was discussed by Bill MacNee (Royal Infirmary, Edinburgh, U.K.), the role of adhesion molecules by Paul Hellewell (Sheffield University, U.K.) and inhibition of phosphodiesterase IV (PDE IV) by Mark Giermbycz (NHLI).

While integrins are heavily involved in leukocyte recruitment and trafficking in inflammatory diseases, there is currently relatively little evidence to substantiate a role for these carbohydrates in COPD. The small

size of pulmonary alveolar capillaries (5-7 μ m in diameter) precludes neutrophil rolling, since the cells need to deform to fit into the capillaries. It is currently believed that their sequestration is an integrin-independent mechanism. In addition, interfering with the effects of β_2 -integrins might compromise host defense mechanisms, as seen in patients with leukocyte adhesion deficiency.

While oxidants normally cause damage via inactivation of regulatory enzymes, the healthy lung contains high concentrations of several antioxidants in epithelial lining fluid. These provide some protection, but depletion of some antioxidants is observed in chronic smokers. Glutathione (GSH) appears to be the most significant of these undergoing initial depletion, followed by a rebound increase due to increased transcriptional regulation of gamma-glutamylcysteine synthetase. It was suggested that these effects might be mediated via tumor necrosis factor.

Vitamin E supplementation has only modest effects *in vivo*, although it is effective *in vitro*. More promising therapeutic approaches appear to be the administration of exogenous superoxide dismutase or catalase or the identification of agents which up-regulate GSH. N-Acetylcysteine, an antioxidant available in some markets, can up-regulate GSH, but only slowly and at unacceptably high oral doses. The development of N-isobutyl-L-cysteine as an inhaled formulation may prove more effective in this regard.

The use of PDE inhibitors, particularly selective PDE IV inhibitors, offers the opportunity of preventing the activation of inflammatory cells, and thus the release of superoxide, LTB₄, IL-8 and elastase. Macrophages, neutrophils and eosinophils all contain several isoforms of PDE IV, albeit in varying ratios. PDE IV inhibitors also inhibit the activation of monocytes and epithelial cells.

Clinical evidence to substantiate a therapeutic role for PDE IV inhibition

in COPD is currently confined to limited data obtained with theophylline. Theophylline treatment for four weeks, at a dose producing a plasma concentration of 9.2 μ g/ml, reduced the neutrophil count, myeloperoxidase and lactoferrin levels in induced sputum. However, it may not have been acting via inhibition of PDE IV.

No other clinical data are currently available, as, until recently, PDE IV inhibitors were only being developed for the treatment of asthma and anhris. Nevertheless, Ariflo (SB-207499; SmithKline Beecham; Fig. 1), a selective PDE IV inhibitor, is now being developed for both indications. Although, in common with most PDE IV inhibitors, this compound induces emesis, it has satisfactorily completed a four-week phase II study in COPD patients. Patients are currently being recruited for a phase III study. It was stated that the phase II study resulted in a significant improvement in FEV₁ and other (unspecified) parameters.

Antismoking therapy

Given the primary causal link between COPD and smoking, it would have been inappropriate not to discuss the subject of antismoking therapy. Martin Jarvis (University College Medical School, London, U.K.) described how pharmacological intervention is the only effective controlled approach. Nicotine replacement therapy has proved effective initially in the form of chewing gum and more recently as nasal sprays, inhalers or transdermal patches. The more recent methods are more effective than gum, but there are still difficulties in continued cessation and smoke of these therapies result in a transferred nicotine dependence.

Alternative approaches are now being investigated. Trials with the α_2 -agonist clonidine produced efficacy comparable to that of nicotine gum, but an unacceptable level of side effects. Concurrent administration of the nicotinic antagonist mecamylamine with the use of nicotine patches is producing promising results. A sustained-release form of the antide-

pressant bupropion has been developed by Glaxo Wellcome and launched in the United States as *Zyban*. This has been found to be superior to the nicotine patch, although in combination they are more effective. It is unclear by what mechanism bupropion is acting to produce these effects.

Concluding remarks

This well-organized meeting provided a good overview of COPD and highlighted our current lack of understanding of the causal mechanisms involved. While smoking is the primary cause, little evidence was presented to suggest what determines whether smokers will subsequently suffer from COPD.

This lack of understanding has doubtless contributed to the pharmaceutical industry's historical neglect of this major disease. However, there now appears to be a significant awareness of the disease and it has now become a major disease target for a number of companies, evidenced by the large contingents of delegates present from several companies.

It was made clear that existing therapies provide modest therapeutic benefits and that both steroids and antibiotics are commonly used, although their efficacy is highly questionable. Few new therapies are in advanced development, but the long-acting tiotropium bromide will facilitate patient compliance. Clinical studies with the long-acting and highly

potent BLT receptor antagonist BIL-294 should clearly establish the significance of LTB₂ in the disease process. In addition, the emergence of clinical data with the PDE IV inhibitor SB-207499 should improve our understanding of the disease process and help to improve the design of future clinical studies.

There is likely to be an explosion of our knowledge of the pathophysiology of COPD over the next few years. Future meetings on this topic will then point to a more optimistic prognosis for COPD patients.

Dr. Peter Norman is Director of Norman Consulting, 18 Pink Lane, Burnham, Buckinghamshire SL1 8JW, U.K.

ARIAD UPDATES STOCKHOLDERS

In a letter to stockholders dated August 14, 1998, Ariad Pharmaceuticals, Inc. provided an update on the company's progress over the past six months.

In the company's signal transduction inhibitor program, Ariad is developing AP-22408, its lead compound that was created using structure-based drug design. AP-22408 was designed to directly block Src, an intracellular protein that Ariad believes is critical to disease progression in osteoporosis. The compound binds to Src with low nanomolar potency, and has demonstrated highly significant evidence of efficacy in a broadly accepted animal model of osteoporosis. Ariad believes that AP-22408 meets the requirements of the second milestone in its strategic partnership for osteoporosis with Hoechst Marion Roussel (HMR).

In addition, the company expects that products based on ARGENTTM (Ariad's Regulated Gene Expression

Technology), a proprietary technology designed to allow control of cellular activities through the administration of small-molecule drugs, will be the first to enter clinical testing. AP-1903, the first ARGENT drug, is currently undergoing preclinical toxicology and pharmacology studies. Initial clinical trials of AP-1903 are being designed to evaluate the safety of the compound when used with ARGENT gene components to treat graft-vs.-host disease in allogeneic bone marrow transplant patients. AP-1903 is expected to enter the clinic before the end of the year.

ARGENT is also being developed as a means to produce orally active therapeutic proteins. In a recent study conducted by Ariad and its joint venture partner Genovo, monkeys received an intramuscular injection of the genetic components of ARGENT and the gene for erythropoietin (EPO). After the genetic material was injected into the muscle of the animals, they received a single dose of a small-molecule dimerizer drug. Upon

drug administration, the monkeys' muscle cells began producing therapeutically relevant levels of EPO, which continued over time. Ariad is currently engaged in further *in vivo* studies, manufacturing scale-up and preclinical testing of the ARGENT orally active therapeutic protein product. The company plans to begin human clinical trials in this program in the first half of next year.

Also during the first half of the year—in March—the Hoechst-Ariad Genomics Center, a joint venture with HMR to identify therapeutic proteins and novel drug targets for small-molecule drug development, reached its first anniversary. The Genomics Center also established its first research collaboration, in July. Ariad scientists are working with the Center for Prevention of Cardiovascular Disease at the Harvard School of Public Health to identify novel genes involved in cardiovascular disease and cancer.